EXHIBIT 9

Reproductive Toxicology 90 (2019) 88–101

Contents lists available at ScienceDirect

Reproductive Toxicology

journal homepage: www.elsevier.com/locate/reprotox

Review

Critical review of the association between perineal use of talc powder and risk of ovarian cancer

Mohamed Kadry Taher[a,b,c,*], Nawal Farhat[a,b,c], Nataliya A. Karyakina[a,b], Nataliya Shilnikova[a,b], Siva Ramoju[a], Christopher A. Gravel[b,c,d], Kannan Krishnan[a], Donald Mattison[a,b,c], Shi-Wu Wen[c,e,f,g], Daniel Krewski[a,b,c]

[a] Risk Sciences International, 251 Laurier Ave W, Suite 700, Ottawa, ON, K1P 5J6, Canada
[b] McLaughlin Centre for Population Health Risk Assessment, Faculty of Medicine, University of Ottawa, 600 Peter Morand Crescent, Ottawa, ON, K1G 5Z3, Canada
[c] School of Epidemiology and Public Health, University of Ottawa, 600 Peter Morand Crescent, Ottawa, ON, K1G 5Z3, Canada
[d] Department of Epidemiology, Biostatistics and Occupational Health, McGill University, 1020 Pine Avenue West, Montreal, QC, H3A 1A2, Canada
[e] OMNI Research Group, Department of Obstetrics and Gynaecology, University of Ottawa Faculty of Medicine, Ottawa, ON, Canada
[f] Clinical Epidemiology Program, Ottawa Hospital Research Institute, Ottawa, ON, Canada
[g] G. Nanhai Hospital, Southern Medical University, Guangzhou, China

ARTICLE INFO

Keywords:
Talc
Ovarian cancer
Perineal
Epidemiological studies
Critical review
Meta-analysis
Toxicological studies

ABSTRACT

Over the past four decades, there has been increasing concern that perineal use of talc powder, a commonly used personal care product, might be associated with an increased risk of ovarian cancer.

Objectives: To critically review all available human epidemiological data on the relationship between perineal use of talc powder and ovarian cancer, with consideration of other relevant experimental evidence.

Methodology: We identified 30 human studies for qualitative assessment of evidence, including 27 that were retained for further quantitative analysis.

Results: A positive association between perineal use of talc powder and ovarian cancer was found [OR: 1.28 (95% CI: 1.20–1.37)]. A significant risk was noted in Hispanics and Whites, in women applying talc to underwear, in pre-menopausal women and in post-menopausal women receiving hormonal therapy. A negative association was noted with tubal ligation.

Conclusion: Perineal use of talc powder is a possible cause of human ovarian cancer.

1. Introduction

Ovarian cancer is a common gynecologic cancer among women in developed countries, occurring at low rates among young women but increasing with age [1]. The annual incidence rate of ovarian cancer during the period 2005–2009 was 12.7/100,000 women, varying by ethnicity. The majority of ovarian cancers are diagnosed at an advanced stage, with 61% having distant metastases at diagnosis. Hereditary risk factors for ovarian cancer, specifically BRCA1 gene mutations, increase the risk above 35 years of age by about 2–3%.

In recent decades, there has been increasing concern that perineal exposure to talc, a commonly used personal care product, might be associated with an increased risk of ovarian cancer. However, the data describing this association is somewhat inconsistent. Perineal application of talc among women varies by geographic location (Supplementary Material I), with prevalence of use generally higher in Canada, the US and the UK compared to Greece, China and Israel [2].

In order to better characterize the potential ovarian cancer risk associated with perineal use of talc, we conducted a critical review and meta-analysis of peer-reviewed human studies on this issue. We also examined available toxicological (in-vivo and in-vitro) studies, which also shed light on possible biological mechanisms of action that might support the biological plausibility of any observed effects in humans.

2. Materials and methods

2.1. Literature search and identification of relevant human studies

A critical, multi-step search strategy was used to identify relevant studies on talc from multiple bibliographic databases, relevant national and international agencies and other grey literature sources. Specifically, we conducted a critical search for all original studies

* Corresponding author at: 600 Peter Morand Crescent, Room 216, Ottawa, ON, K1G 5Z3, Canada.
E-mail address: Mohamed.Taher@uOttawa.ca (M. Kadry Taher).

https://doi.org/10.1016/j.reprotox.2019.08.015
Received 20 November 2018; Received in revised form 21 August 2019; Accepted 23 August 2019
Available online 28 August 2019

Table 1
Characteristics and overall findings of all included studies (N = 30).

Study (Location)	Sample Size (Cases/ Controls or Cases/ Total Cohort)	Age (Years)	Subgroup Analyses	Exposure-Response Assessment	Overall Author Conclusion	NOS[a]
Case-control studies						
Booth et al.* (1989), UK [9]	235/451	Range: 20-65 Mean: 52.4 (cases); 51.4 (controls)	Frequency	No trend found	Possible association with > weekly use.	5
Chang and Risch (1997), Canada [10]	450/564	Range: 35-79 Mean: 57.2 (cases); 57.5 (controls)	Ever use Frequency Duration Time of use Type of use Pelvic surgery Histology	Possible exposure-response with frequency and duration of use	Positive association	7
Chen et al.* (1992), China [11]	112/224	Mean: 48.5 (cases); 49.0 (controls)	Ever use;	No trend analysis conducted	Positive association with use > 3 months	6
Cook et al. (1997), USA [12]	313/422	Range: 20-79	Ever use Duration Type of use Histology Lifetime applications	No trend found	Positive association.	7
Cramer et al. (1982), USA [13]	215/215	Range: 18-80 Mean ± SD: 53.2 ± 1.0 (cases); 53.5 ± 1.0 (controls)	Ever use Type of use Pelvic surgery	No trend analysis conducted	Positive association	6
Cramer et al. (2016), USA [14]	2,041/2,100	Range: 18-80	Ever use; Frequency; Duration; Type of use; Histology; Type of powder; Pelvic surgery; Ethnicity; Age at first use; Time since last exposure;	Significant trend for years since exposure, frequency and duration of use, and number of lifetime applications	Positive association	7
Gates et al. (2008), USA [15]	New England Case Control (NECC): 1,175/1,202 Nurses' Health Study (NHS): 210/600	Mean ± SD: 51 ± 13 (NECC); Mean ± SD: 51 ± 8 (NHS)	Ever use; Frequency;	Significant trend for frequency of use	Positive association	7
Godard et al. (1998), Canada [16]	153/152	Mean: 53.7	Ever use; Sporadic/familial	No trend analysis conducted	No association	5
Green et al. (1997), Australia [17]	824/860	Range: 18-79	Ever use; Pelvic surgery;	No trend found	Positive association	7
Harlow et al. (1989), USA [18]	116/158	Range: 20-79	Ever use; Type of use; Type of powder;	No trend analysis conducted	No association	7
Harlow et al. (1992), USA [19]	235/239	Range: 18-76	Ever use; Frequency; Duration; Type of use; Method of use; Histology; Tumor grade; Type of powder; Lifetime applications; Age of first use; Pelvic surgery;	Significant trend for monthly frequency of use	Positive associations in certain subgroups (talc used before 1960, women < 50 years old, women with 1 or 2 live births)	7
Hartge et al. (1983), USA [20]	135/171	Mean: 52.1 (cases); 52.2 (controls)	Ever use;	No trend analysis conducted	No association	5
Kurta et al. (2012), USA [21]	902/1,802	Range: No range reported (age 25+)	Ever use;	No trend analysis conducted	Positive association	6
Langseth & Kjaerheim (2004), Norway [22]	46/179	Not reported	Ever use,	No trend analysis conducted	No association	4
Merritt et al. (2008), Australia [23]	1,576/1,509	Range: 18-79 Mean: 57.8 (cases); 56.4 (controls)	Ever use; Duration; Histology; Pelvic surgery; Age at diagnosis;	No trend found	Positive association strongest for serous and endometrioid subtypes.	7
Mills et al. (2004), USA [24]	249/1,105	Mean ± SD: 56.6 (cases); 55 (controls)	Ever use; Frequency; Duration; Year of first use; Histology; Pelvic surgery; Time of use; Tumor behavior; Cumulative use;	No trend found	Positive association for invasive and serous invasive tumors.	6
Moorman et al. (2009), USA [25]	African-American: 143/189; White 943/868	Range: 20-74	Ever use; Ethnicity;	No trend analysis conducted	No association	6
Ness et al. (2000), USA [26]	767/1,367	Range: 20-69	Ever use; Duration; Method of use;	No trend found	Positive association for any method of use.	6

(*continued on next page*)

Table 1 (*continued*)

Study (Location)	Sample Size (Cases/ Controls or Cases/ Total Cohort)	Age (Years)	Subgroup Analyses	Exposure-Response Assessment	Overall Author Conclusion	NOS[a]
Rosenblatt et al. (1992), USA [27]	77/46 (analyzed)	Range: ≤30 – 80≥	Ever use; Duration; Type of use; Pelvic surgery;	Positive trend for duration of use since tubal ligation	Possible association	4
Rosenblatt et al. (2011), USA [28]	812/1,313	Range: 35-74	Ever use; Lifetime number of applications; Duration; Year of first use; Age of first use; Age of last use; Time of use; Type of use; Histology;	No trend found	Possible association	7
Schildkraut et al. (2016), USA [29]	584/745	Range: 20-79	Ever use; Frequency; Duration; Histology; Lifetime applications; Menopausal status;	Significant trend with frequency and duration of use, and number of lifetime applications	Positive association	8
Tzonou et al. (1993), Greece [30]	189/200	Range: < 70	Ever use;	No trend analysis conducted	No association	5
Whittemore et al. (1988), USA [31]	188/539	Range: 18-74	Ever use; Frequency; Duration; Type of use; Pelvic surgery;	No trend found	Could neither implicate nor exonerate talc as an ovarian carcinogen	4
Wong et al. (1999), USA [32]	462/693	Mean: 54.9	Ever use; Type of use; Duration; Pelvic surgery;	No trend found	No association	4
Wu et al. (2015), USA [33]	1,701/2,391	Range: 18-79	Ever use; Ethnicity;	No trend analysis conducted	Positive association among Hispanics and non-Hispanic whites, but not African Americans.	7
Wu et al. (2009), USA [34]	609/688	Range: 18-74	Ever use; Frequency; Duration; Type of use; Histology; Time of use; Cancer stage;	Significant trend for frequency and duration of use, and number of lifetime applications	Positive association	7
Cohort studies						
Gates et al. (2010) *, USA [35]	797/108,870	Range: 30-55	≥/week vs < 1/week; Histology;	No trend analysis conducted	Possible association that varies by histological subtype. No association with mucinous tumors.	7
Gertig et al. (2000), USA [36]	307/78,630	Range: 30-55 (at cohort entry)	Ever use; Frequency; Histology; Race;	No trend found	Possible association (modest increase for serous invasive subtype)	5
Gonzalez et al. (2016), USA [37]	154/41,654	Range: 35-74 Median: 57.8	Ever use; Time of use;	No trend analysis conducted	No association	6
Houghton et al. (2014), USA [38]	429/61,285	Range: 50-79 Mean: 63.3	Ever use; Duration; Type of use; Histology;	No trend found	No association	7

* Study not included in the meta-analysis because of overlap among the study populations.

[a] Newcastle-Ottawa Scale (NOS) score for each of the listed studies as assessed in our review.

involving human subjects that examined the association of genital/perineal use of talc powder and risk of ovarian cancer, including studies identified in a previous review by Berge et al. [3]. This review followed the PRISMA guidelines, and more specific guidance provided by the Cochrane Collaboration [4] (see Supplementary Material II, III and IV for details on identification of human studies).

Included studies were individually evaluated and scored by two reviewers (MT and NF), as summarized in Table 1 and detailed in Supplementary Material VI and VII. Excluded human studies and reasons for exclusion are shown in Supplementary Material IV. Studies included in previous reviews by both Berge et al. [3] and Penninkilampi et al [5] are compared in Supplementary Material I.

The quality of included studies was assessed using the Newcastle-Ottawa Scale (NOS) [6] as detailed in Supplementary Material V. We used a cut-off point of 7+ stars to represent studies of higher quality (maximum is 9 stars). This cutoff point has been adopted in the literature as indicative of high-quality observational studies [7,8].

2.2. Literature search and identification of relevant non-human studies

We conducted a critical review of non-human studies selected from 3 major bibliographic databases (Medline, EMBASE and Toxline) to identify potentially relevant animal studies on carcinogenic effect of the poorly soluble talc particles following perineal or intravaginal exposure. Studies that focused on any type of cancer, including ovarian cancer, and perineal exposure were considered. All retrieved studies were examined for relevance and reliability. The initial search identified 1165 studies, including, but not limited to, all studies listed in the 2010 IARC report [2]. After level 1 (title and abstract) and level 2 (full text) screening), 51 references were retained for further review. Of those, 15 were considered relevant to this review. Full details of search strategy, inclusion and exclusion criteria, and included studies are given in Supplementary Material VIII, IX and X, respectively.

Studies were classified into one of the following four categories of reliability: 1) reliable without restriction, 2) reliable with restrictions, 3) not reliable and 4) not assignable. Additionally, category (5) is assigned to special studies focusing on pharmacologic or mechanistic investigations.

2.3. Hazard characterization

Epidemiological studies included in the critical review were qualitatively assessed to examine their potential to inform the analysis. Findings from these studies were evaluated with respect to study design, exposure and outcome ascertainment, as well as potential sources of bias and confounding.

In evaluating evidence from animal studies, consideration was given to the form and relevance of the test material, exposure circumstances, animal species/cell system, and health effects studied. Consistency of results among comparable studies and of results in different sexes, species and strains was considered. Evaluation of relevance of studies in laboratory animals to humans was supported by toxicokinetic information in humans and animals, and by mechanistic data from 14 relevant in-vitro studies.

Animal studies were evaluated for evidence on the association between perineal application of talc and ovarian cancer. Additional information on mechanism of action and toxicokinetics obtained from in-vivo and in-vitro studies were used in evaluating biological plausibility of any observed effects.

2.4. Quantitative meta-analysis

We conducted a meta-analysis of the risk of ovarian cancer in relation to perineal use of talc using quantitative risk estimates reported in 27 original studies, comprising three cohort studies and twenty-four case-control studies (included in Table 1). Studies that had analyzed overlapping study populations were assessed on a case-by-case basis for inclusion into the meta-analysis. The level of detail in the reported findings, including sample size and publication date, were considered when deciding which study to include in the case of overlap (Supplementary Material XI).

Maximally adjusted odds ratios (ORs), hazard ratios (HRs) or relative risks (RRs) – measures that are largely comparable because of the relatively low rate of occurrence of ovarian cancer – were extracted from the original studies. Details of the meta-analytic methods are provided in Supplementary Material XI.

3. Results

3.1. Evidence from human studies

The multiple database search for original human studies yielded 656 references. Although a grey literature search yielded another 477 references, only 5 were judged relevant the present analysis. Automatic followed by manual removal of duplicates identified 282 references for screening and review.

Multi-level screening and full-text examination resulted in the in the inclusion of 30 studies for further qualitative/quantitative analyses (Supplementary Materials III and IV). A detailed PRISMA flow diagram is shown in Fig. 1 [9]. Key characteristics of the included 26 case-control studies and four cohort studies are summarized in Table 1. This include study location, sample size, age, performed subgroup analyses, exposure-response assessment, overall conclusion (as reported by the authors, and the Newcastle Ottawa Scale (NOS) score.

Twenty-one of the thirty studies were carried out in the USA, with the remaining studies conducted in Europe (n = 4), Canada (n = 2), Australia (n = 2) and China (n = 1). Forty percent (n = 12) of the studies were relatively recent, published in the last decade, with the remaining studies published between 1982 and 2006. The study populations generally included adult women. Several studies analyzed data from populations initially recruited for other purposes, such as the Nurses' Health Study (NHS) [10–12] and Women's Health Initiative (WHI) [13].

The number of ovarian cancer patients analyzed varied from as few as 46 cases [14] to 22,041 cases per study [10]. Twenty-seven out of the 30 included studies assessed the association between ever use of perineal talc use and ovarian cancer. Subgroup analyses examining the effect of frequency and duration of use, type of use, period of use and other factors varied among these studies (Table 2).

Sixty three percent (n = 19) of the studies concluded the presence of a positive association between perineal exposure to talc powder and ovarian cancer risk [10,11,15–31]. Ten studies concluded the absence of an association [12–14,32–38]. Only one study could not reach a clear conclusion on the presence or absence of an association [39]. Many of the included studies reported variability in some of the analyzed subgroups regarding possible association between exposure to talk powder and risk of ovarian cancer. Supplementary Material VI presents the findings and details of all the studies included in our review, while Supplementary Material VII summarizes the strengths and limitations of each of these studies as identified by the original study authors and by us.

3.2. Evidence from Non-Human studies

After removal of duplicates, the bibliographic database searches on non-human studies initially yielded 1165 references. The 48 retained animal studies focusing on the carcinogenicity of talc, mechanism of action, and toxicokinetics are summarized in Supplementary Material VIII, IX and X.

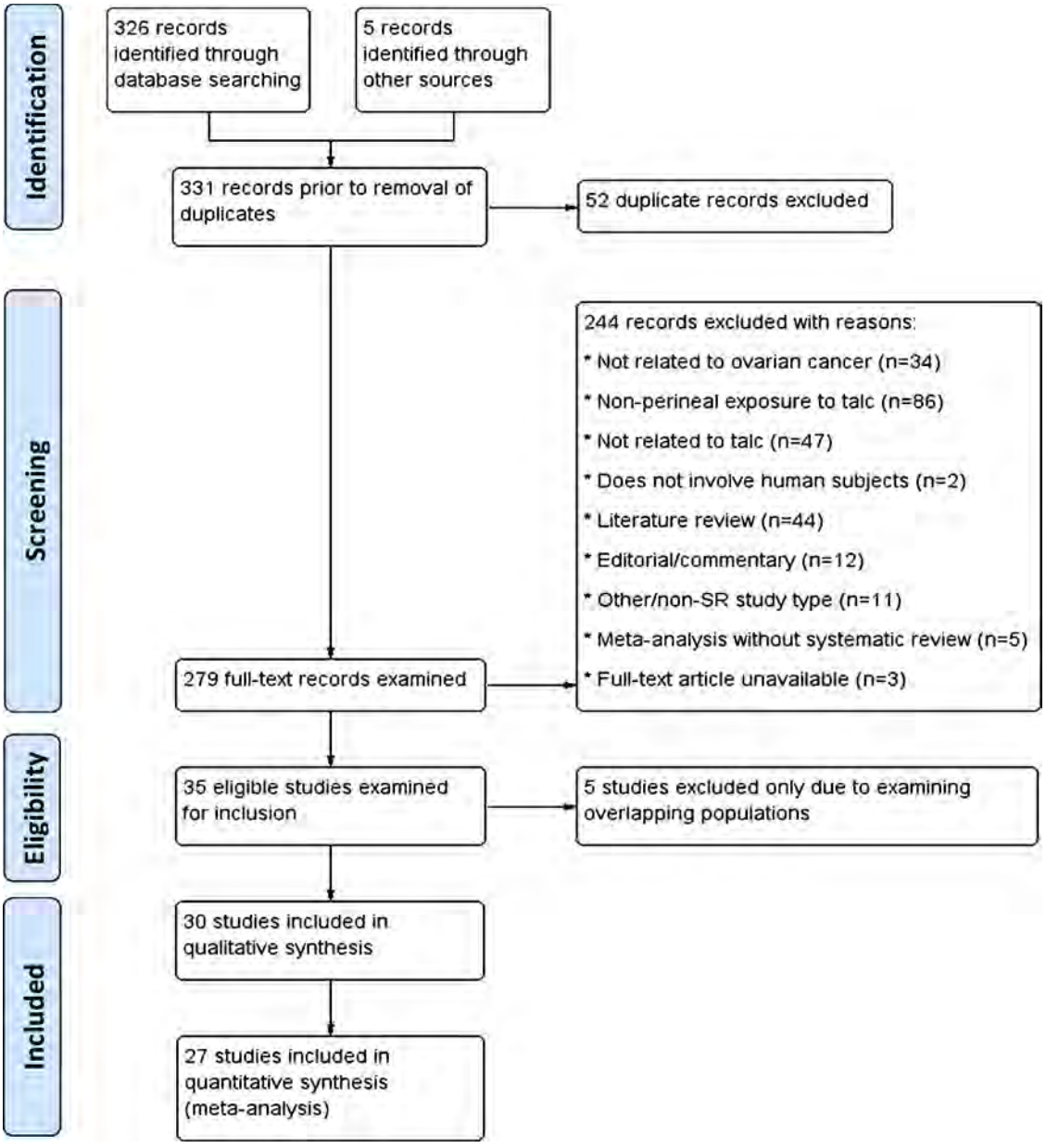


Fig. 1. PRISMA flow diagram.

3.3. Hazard characterization

3.3.1. Evidence from human studies

The case-control studies generally included adult women participants. Cases were commonly selected from registries or hospital records, and included all eligible subjects within a specific geographic region and diagnosed with ovarian cancer within a predetermined time period. Controls were generally matched to cases by age and residence. All the included studies compared the risk of ovarian cancer in ever vs never users of talc (perineal application). However, several of the studies also included subgroup analyses to examine the potential effect of frequency of use, duration of use, tumor histology, ethnicity, method of use, lifetime number of applications, year of first use, and menopausal status. Some authors concluded that the risk of ovarian cancer is limited to [or stronger in] certain subgroups (weekly talc users, premenopausal women) or for specific histology types (notably serous tumors).

Studies reported effect estimates adjusted for a variety of potential confounders (see detailed tables in Supplementary Material VI and VII). Age and parity were considered the two most important variables that could introduce potential bias, based on prior literature: few studies reported findings that were not adjusted for these two variables. As many of the studies only reported on the ovarian cancer risk assessing only one exposure category (comparing only ever vs never users of talc), exposure-response analyses were not done in all studies. When conducted, findings from trend analyses were not consistent.

3.3.2. Evidence from non-human studies

The following aspects were considered in assessment of ovarian cancer and perineal exposure to talc:

- Evidence on ovarian cancer reported in animal studies; and
- Potential hazards arising from the physical and chemical properties of talc, including potential structure-activity relationship indicative of carcinogenic potential;
- The toxicokinetics of talc and the ability to migrate from the perineal area to ovaries and quantity at the actual target site (the tissue dose);
- Findings from in vitro studies suggestive of mechanism of action of carcinogenic effect.

Table 2
Results of the subgroup analysis of talc exposure and ovarian cancer.

Outcome or Subgroup	Studies	Effect Estimate [95% CI]	Heterogeneity I^2 Statistic [p-value]
1 ***Talc use***			
Ever vs. Never	27	1.28 [1.20, 1.37]	33% [< 0.00001]
Ethnicity	3		77% [0.08]
African Americans	3	1.67 [0.90, 3.10]	48% [0.10]
Hispanics	2	1.70 [1.17, 2.47]	0% [0.005]
Whites	3	1.28 [1.11, 1.49]	56% [0.001]
Asians	1	0.04 [0.01, 0.16]	N/A
2 ***Study Assessment***			
●	27		33% [< 0.00001]
○ Study Design			
Case-Control	24	1.32 [1.24, 1.40]	22% [< 0.00001]
Cohort	3	1.06 [0.90, 1.25]	17% [0.49]
●	24		22% [< 0.00001]
○ Type of Controls			
Hospital-based	4	0.96 [0.78, 1.17]	0% [0.66]
Population-based	19	1.34 [1.27, 1.41]	0% [< 0.00001]
Combined	1	1.45 [0.81, 2.60]	N/A
●	27		33% [< 0.00001]
○ Quality Score (NOS)			
NOS > =7	12	1.32 [1.25, 1.40]	0% [< 0.00001]
NOS < 7	15	1.21 [1.05, 1.39]	47% [0.009]
●	27		33% [< 0.00001]
○ Publication Year			
1980-1989	4	1.23 [0.81, 1.88]	66% [0.33]
1990-1999	8	1.30 [1.13, 1.50]	24% [0.0003]
2000-2009	8	1.25 [1.14, 1.37]	18% [< 0.00001]
2010 and beyond	7	1.31 [1.18, 1.45]	44% [< 0.00001]
3 ***Talc Exposure***			
●	7		35% [< 0.00001]
○ Frequency of Use			
Low	5	1.22 [0.96, 1.54]	54% [0.10]
Medium	2	1.22 [0.98, 1.53]	0% [0.08]
High	7	1.39 [1.22, 1.58]	23% [< 0.00001]
●	6		5% [0.0008]
○ Duration of Use			
< 10 Years	5	1.22 [1.03, 1.45]	0% [0.02]
10 - < 20 Years	2	1.42 [1.02, 1.99]	0% [0.04]
20+ Years	2	1.19 [0.71, 1.98]	75% [0.51]
●	13		52% [0.001]
○ Method of Use			
Sanitary Napkin	11	1.12 [0.91, 1.39]	50% [0.29]
Diaphragm	10	0.87 [0.72, 1.05]	25% [0.14]
Underwear	2	1.70 [1.27, 2.28]	0% [0.0004]
Male Condom	3	0.99 [0.73, 1.32]	0% [0.92]
4 ***Tumor Histology***			
●	8		23% [< 0.00001]
○ Tumor Histology			
Serous	7	1.38 [1.22, 1.56]	0% [< 0.00001]
Mucinous	5	1.05 [0.85, 1.29]	23% [0.41]
Endometrioid	6	1.39 [1.05, 1.82]	2% [0.03]
Clear Cell	1	0.63 [0.15, 2.65]	
5 ***Tumor Behavior***			
●	4		0% [< 0.00001]
○ All Grades			
All Invasive	3	1.38 [1.15, 1.65]	0% [0.0004]
All Borderline	4	1.43 [1.08, 1.89]	19% [0.01]
●	5		0% [< 0.00001]
○ Serous			
Serous Invasive	5	1.32 [1.13, 1.54]	24% [0.00004]
Serous Borderline	3	1.39 [1.09, 1.78]	0% [0.008]
●	3		38% [0.40]
○ Mucinous			
Mucinous Invasive	2	1.34 [0.48, 3.79]	70% [0.58]
Mucinous Borderline	3	1.18 [0.76, 1.82]	34% [0.46]
●	1		N/A
○ Endometrioid			
Endometrioid Invasive	1	1.38 [1.06, 1.80]	
●	1		N/A
○ Clear Cell			
Clear Cell Invasive	1	1.01 [0.65, 1.57]	
6 ***Modifiers***			
●	2		78% [0.007]
○ Menopausal State			
Pre-menopausal	2	1.42 [1.16, 1.75]	0% [0.0008]

(*continued on next page*)

Table 2 (*continued*)

Outcome or Subgroup	Studies	Effect Estimate [95% CI]	Heterogeneity I^2 Statistic [p-value]
Post-Menopausal (HT)	2	2.28 [1.72, 3.01]	0% [< 0.00001]
Post-Menopausal (no HT)	2	1.05 [0.84, 1.32]	25% [0.66]
●	7		78% [0.35]
○ Pelvic Surgery			
Tubal Ligation	3	0.64 [0.45, 0.92]	19% [0.02]
Hysterectomy	4	0.89 [0.54, 1.46]	61% [0.65]
Combined	4	1.06 [0.78, 1.42]	61% [0.72]

*NOS: Newcastle-Ottawa Scale for quality scoring of observational studies (maximum is 9 stars).
Low: Once daily for 1 – < 10 days/month; **Medium: Once daily for 10–25 days/month; **High:** Once daily for > 25 days/month.

While the limited data from the animal studies that considered various routes of talc administration are inconsistent [40–45], there are observations from in vivo and in vitro studies which support the potential for local carcinogenic action of talc particles on fallopian, ovarian and peritoneal epithelium [26,46–52].

The results from the *in vitro* studies are informative for mechanisms of action of possible carcinogenicity. Smith and colleagues [53] identified 10 key characteristics (KCs) commonly exhibited by established human carcinogens.

Oxidative stress (KC 6) and inflammation (KC 5) in cell cultures induced by talc have been reported by several authors [47], corresponding to two of the 10 key characteristics (KCs) described by Smith et al. [53]. Several authors suggested additional potential mechanisms of action through cell proliferation (KC 10) and changes in gene expression, presumably facilitated by oxidative stress and dysregulated antioxidant defense mechanisms [48,54].

Chronic perineal or vaginal exposures of animals to talc do not directly affect ovulation or steroidal hormone levels, but can induce chronic local inflammation, which has been suggested as a risk factor for ovarian cancer [55]. Mechanism of action studies suggested that talc can complex iron on the surface and disrupt iron homeostasis, associated with oxidant generation, macrophage distress and leukotriene released by macrophages in the surrounding cells resulting in a chronic inflammatory response which could possibly contribute to tumor promotion in both animals and humans [47,49,50].

The changes seen in cultured cells after exposure to talc particles [49,50] are consistent with those inflammatory and proliferative processes in the lungs seen in laboratory animals after inhalation exposure in a 1993 study conducted by the US National Toxicology Program [46]. In female rats, hyperplasia of alveolar epithelium was associated with inflammatory response and occurred in or near foci of inflammation [46]. The severity of the fibrous granulomatous inflammation in the lungs increased with increased talc concentrations and exposure duration and a significant association was observed between inflammation and fibrosis in the lungs and the incidence of pheochromocytomas in this study [46]. Overall, the available experimental data suggests that long-term irritation, followed by oxidative stress and chronic inflammation, may be involved in local carcinogenic effects of talc in the ovaries.

Local inflammation of the epithelial ovarian surface in rats following by injection of a suspension of talc particles resulted in the development of foreign body granulomas surrounding talc particles and large ovarian bursal cysts [52]. It is generally accepted that benign and malignant ovarian epithelial tumors arise from surface epithelium and its cystic derivatives, and surface epithelial cysts have a greater propensity to undergo neoplasia than does the surface epithelium itself [56]. Evidence of neoplasms of epithelial origin, nuclear atypia, or mitotic activity in the surface epithelium was not found in this study; however, focal areas of papillary changes in the surface epithelium consistent with the histological signs of premalignancy were observed in 40% of treated animals [52].

Structure-activity relationships can provide useful information for assessing potential carcinogenicity. Although structure-activity models predict that poorly soluble particulates such as carbon black and titanium dioxide may be potentially carcinogenic [2], the extension to talc particles is not immediate.

Although inconsistent, there is some evidence that talc particles may migrate in the genital tract of animals [57–60]. Some studies have reported lack of migration of neutron-activated talc from the vagina to the ovaries in cynomolgus monkeys [57], but talc particles were identified in the ovaries of rats that received intrauterine instillation of talc [59]. Radioactivity was not found in the ovaries of rabbits dosed intravaginally with tritium-labelled talc, but was detected in cervix and fallopian tubes [58–60]. Henderson and colleagues [61] examined human tumor tissue of patients with ovarian and cervical tumors, detecting talc particles in histological samples from 10 of 13 ovarian tumors, 12 of 21 cervical tumors, and 5 of 12 normal ovarian tissue samples [61].

Historically, the concern for talc carcinogenicity has been associated with its contamination by asbestos fibers (tremolite) [62], which is considered carcinogenic to humans [2]. In response to this concern, talc, including baby powder, available in the US, contains only U.S. Pharmacopeia (USP) grade pure talc [63]. Talcum powder has been asbestos-free since the 1976 where the specifications for cosmetic talc were developed [64].

3.4. Meta-Analysis

The use of genital talc was associated with a significant increase in the risk of epithelial ovarian cancer, with an overall odds ratio [OR] based on our meta-analysis of 1.28 (95% confidence interval [CI]: 1.20–1.37 P < 0.0001, I^2 = 33%), as presented in Fig. 2. This result is comparable to those of earlier meta-analyses conducted by other investigators [3,5,65–67] as shown in Supplementary Material I.

An increased risk is more apparent in Hispanics and Whites, in women applying talc to underwear, in pre-menopausal women and post-menopausal women receiving hormonal therapy, as well as for the serous and endometrioid types of ovarian cancer (Table 2 and Supplementary Material XI). A negative association was noted with tubal ligation. Our analysis pooled risk estimates from 27 original studies including 3 cohort studies and 24 case-control studies, spanning across four decades (1982–2016) and including a total of 16,005 cases and 201,881 controls from different ethnicities.

In assessing heterogeneity among included studies, most subgroup analyses reported an I^2 statistic ranging between 0%–40%, which will have only a minimal impact on the analysis [4]. Only three subgroup analyses (ethnicity, menopausal state, and pelvic surgery) reported an I^2 statistic of 77%–78%, where considerable heterogeneity might have had an impact on the results [4]. (See Table 2 and Supplementary Material XI for a listing of I^2 statistic values for the different subgroup analyses)

Whereas case-control studies showed a significant increase in the risk of ovarian cancer for “ever vs never” users of talc powder [OR: 1.32 (95% CI: 1.24–1.40), P < 0.00001, I^2 = 22%], cohort studies failed to show a significant increase in risk [OR: 1.06 (95% CI: 0.9–1.25), P = 0.49, I^2 = 17%]. Thirteen out of 24 case-control studies (54%)

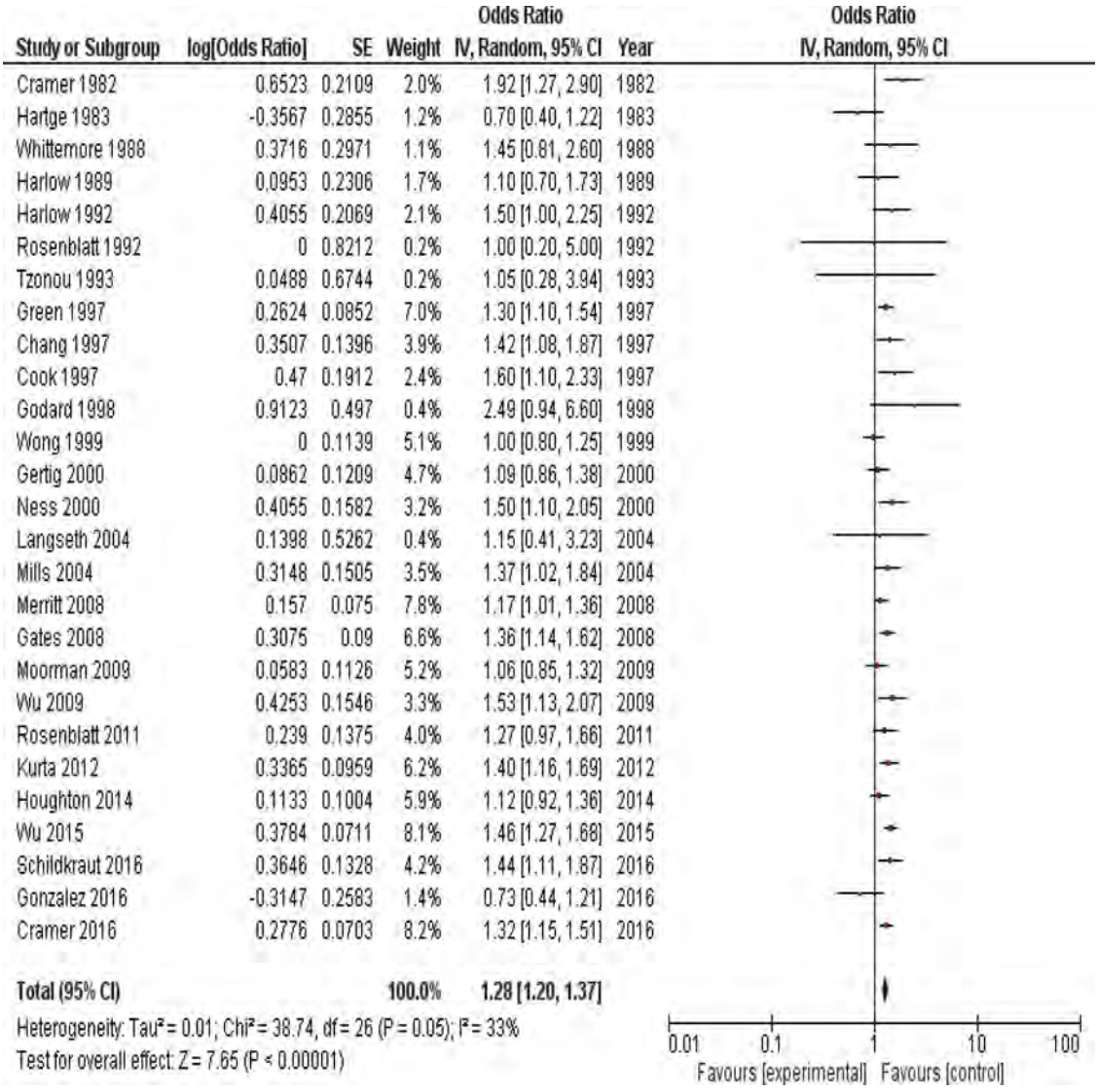


Fig. 2. Forest plot of the meta-analysis results on perineal use of talc and risk of ovarian cancer.

showed a statistically significant association, whereas none of the 3 cohort studies showed a significant overall association between ever vs never genital talc exposure and risk of ovarian cancer.

Subgroup analysis by study quality using the Newcastle Ottawa Scale (NOS ≥ 7 vs NOS < 7) did not show any significant differences in the overall pooled risk estimate. Similarly, there were no differences among subgroup analysis conducted by decade of publication. A significant association was observed for population-based studies [OR: 1.34 (95% CI: 1.27–1.41), P < 0.00001, I^2 = 0%], but not for enlisting hospital-based controls [OR: 0.96 (95% CI: 0.78–1.17), P = 0.66, I^2 = 0%].

We conducted influence analysis to examine the impact of individual studies on the results of our meta-analysis. No appreciable changes were observed regarding the overall association of perineal talc exposure and the risk of ovarian cancer in response to the exclusion of any single study. Detailed results from the influence analysis are provided in Supplementary Material XI.

Subgroup analysis based on ethnicity indicated that Hispanic women using talc showed the most significant increase in risk of ovarian cancer [OR: 1.70 (95% CI: 1.17–2.47), P = 0.005, I^2 = 0%], followed by White women [OR: 1.28 (95% CI: 1.10–1.49], P = 0.001, I^2 = 56%). African-American women showed an elevated, yet non-significant association with ovarian cancer in [OR: 1.67 (95% CI: 0.90–3.10), P = 0.1, I^2 = 48%].

Analyzing exposure by frequency of talc use, talc exposure was stratified into three groups: high (once daily for > 25 days/month), medium (once daily for 10–25 days/month) and low (once daily for 1– < 10 days/month). The OR for the high-use group was higher in the high-use group compared to the other two groups (medium and low-use groups). Duration of talc use was stratified into three groups: < 10 years, 10 – < 20 years, and 20+ years. The overall odds ratio of the < 10 years' group was lower than the OR for the 10 – < 20 years' group. On the other hand, the OR for the 20+ years' group was lower and not statistically significant. However, this OR was based on two studies that showed considerable heterogeneity (I^2 = 75%). Examining the method of application of talc, application to the underwear subgroup had a statistically significant OR, which was the highest among all subgroups. Diaphragm use showed an expected, yet non-significant, negative association with ovarian cancer, which may be due to its action blocking the ascent of talc particles up the reproductive tract.

Pooled risk estimates were statistically significant for two histological types of ovarian cancer: serous tumors [OR: 1.38 (95% CI: 1.22–1.56), P < 0.00001, I^2 = 0%] and endometrioid tumors [OR: 1.39 (95% CI: 1.05–1.82), P = 0.03, I^2 = 2%]. The mucinous type showed a non-significant association [OR: 1.05 (95% CI: 0.85–1.29), P = 0.41, I^2 = 23%], while there were not sufficient studies to examine the other types of ovarian cancers. Regarding tumor behavior, there

was no appreciable difference between invasive [OR: 1.38 (95% CI: 1.15–1.65), P = 0.0004, I^2 = 0%] and borderline [OR: 1.43 (95% CI: 1.08–1.89), P = 0.01, I^2 = 19%] grades of ovarian cancer. Borderline serous tumors showed slightly greater risk [OR: 1.39 (95% CI: 1.09–1.78), P = 0.008, I^2 = 0%] compared to the serous invasive grade [OR: 1.32 (95% CI: 1.13–1.54), P = 0.0004, I^2 = 24%], while both showed a significant association with perineal talc exposure. However, the mucinous tumors showed a non-significant association with talc exposure, with invasive grades being associated with a greater risk [OR: 1.34 (95% CI: 0.48–3.79), P = 0.58, I^2 = 70%] compared to the borderline grade [OR: 1.18 (95% CI: 0.76–1.82), P < 0.46, I^2 = 34%].

Among post-menopausal women, those receiving hormonal therapy showed the greatest risk [OR: 2.28 (95% CI: 1.72–3.01), P < 0.00001, I^2 = 0%], followed by pre-menopausal women [OR: 1.42 (95% CI: 1.16–1.75), P = 0.0008, I^2 = 0%], and then post-menopausal women not receiving hormonal therapy [OR: 1.05 (95% CI: 0.84–1.32), P = 0.66, I^2 = 25%]. This subgroup analysis suggests that hormonal factors, especially estrogens influence the risk of developing ovarian cancer among postmenopausal women who have perineal talc exposure.

Women with prior ligation of the Fallopian tubes showed a significant reduction in risk [OR: 0.64 (95% CI: 0.45 to 0.92), P = 0.02, I^2 = 19%] against ovarian cancer compared to hysterectomy [OR: 0.89 (95% CI: 0.54–1.46), P = 0.65, I^2 = 61%], whereas both surgeries combined showed no effect [OR: 1.06 (95% CI: 0.78–1.42), P = 0.72, I^2 = 61%]. This might be attributed to the fact that tubal ligation is usually performed at an earlier age, thus preventing entry of talc into the reproductive tract earlier and prolonged exposure to talc, compared to hysterectomy that is performed later in life where a higher exposure has already taken place. In a recent meta-analysis [68], the authors reported a negative association of tubal ligation (27 studies) and hysterectomy (15 studies) with the risk of ovarian cancer: this negative association was more apparent in women who had the surgery at an earlier age. A highly plausible mechanism for this association, as suggested by the authors, involves blocking of ascent of agents such as talc to the ovaries.

A summary of results of our meta-analysis is shown in Table 2. Forest plots of all sub-group analyses are provided in Supplementary Material XI.

3.5. Exposure-response assessment

The effect of increasing frequency or duration of perineal use of talc and the risk of ovarian cancer was assessed in the majority of the studies included in this review. Conflicting findings were reported on the nature of the exposure-response relationship: 11 studies concluded that there is no exposure-response, five studies reported a significant positive trend with either frequency or duration of talc use, and two studies concluded that there might be an exposure-response. The remaining twelve studies did not perform or report on trend analyses.

Findings from the seven studies that indicated a potential increased risk of ovarian cancer associated with increasing use of talc are presented in Table 3. The study by Cramer et al. [10] provides the strongest evidence of an exposure-response relationship and could be considered as a key study for exposure-response assessment. The data used in this study were generated from the Nurses' Health Study originally conducted by Belanger et al. [69], a well-designed high quality cohort study of the factors affecting women's health. The results of this study show an increased risk of ovarian cancer at the three highest exposure categories in this study, with the risk at the lowest exposure level [OR: 1.15 (95% CI: 0.89 to 1.47)] being numerically, although not significantly, elevated. Other studies in Table 3 have provided findings in support of an exposure response based on increasing number of talc applications [22,29,31].

In order to permit more direct comparisons of the exposure-response findings from these studies, and whenever the original study data permits, we standardized exposure measurements into talc-years as shown in Fig. 3. Data points were selected from studies after excluding potential data points that are lacking precise information on the level of exposure to talc. The mid-point of the exposure categories in the exposure-response studies was used for exposure-response assessment.

Overall, the graphical results shown in this Fig. 3 suggest a possible increasing trend in ovarian cancer risk with increasing cumulative exposure to talc; however, there is also a high degree of uncertainty surrounding many of the individual risk estimates. (A formal statistical test for trend was not attempted because of the high degree of heterogeneity among studies noted previously in our meta-analysis discussed in Section 3.4)

4. Discussion

The present analysis of the association between perineal use of talc powder and ovarian cancer risk considered four decades of scientific work exploring the epidemiological associations and non-human studies. The motivation for this review is based on two questions: what do human epidemiology studies of perineal talc exposure reveal about potential ovarian carcinogenicity, and what do in-vitro and in-vivo studies suggest about potential mechanisms of toxicity?

A critical review of the human epidemiology studies was conducted to address the first question. Thirty observational epidemiologic studies were identified and assessed for quality using the NOS [6]. In parallel with the review of human epidemiological evidence, a critical review of evidence exploring in- vivo and in-vitro toxicology data on talc was conducted. Although animal studies have limited relevance to the investigation of carcinogenicity of talc following perineal exposure, experimental evidence from both animal and in vitro studies can accurately represent the cellular and molecular changes associated with the initiation and progression of human ovarian cancer following perineal exposure to talc.

The available animal evidence provides some insights concerning possible mechanisms of talc toxicity, including oxidative stress, immune system alterations and inflammatory responses. However, it also indicates that talc is not genotoxic. In total, the epidemiology studies suggest that perineal exposure to talc powder is a possible human ovarian carcinogen but there are concerns that the actual exposure experienced by these women over the past 40–50 years is not well understood. As reported by Langesth and colleagues [65], there had been some concern that asbestos-contaminated talc powder that was produced prior to 1976 might have been a confounder; however, the similarity of findings between studies published prior to and after this point suggests asbestos contamination does not explain the positive association between perineal use of talc powder and risk of ovarian cancer [25,26].

Human observational studies have inherent limitations that could bias the findings. Potentially important sources of bias reported in the included studies include: 1) selection bias due to low response rates from cases and controls or from limiting subjects to English-speaking women of two specific races, and 2) exposure misclassification due to recall bias inherent in case control studies. Other limitations included small sample sizes in some studies, small numbers of subjects in subgroup analyses, lack of information on duration of talc use in many studies that only compared ever vs never users, as well as lack of information on the talc content of the different brands of genital powders used. In two of the three cohort studies, the follow-up period between exposure assessment and end of study could have been inadequate to detect a potential association between talc exposure and ovarian cancer. Houghton et al. [13] reported a mean follow up of 12.4 years, while Gates et al. [11] followed a cohort of women for 24 years. However, Gertig et al. [12] and Gonzalez et al. [38] noted that one of their main limitations is the relatively short follow up periods that may not be adequate to detect a potential association between talc exposure and ovarian cancer. For example, studies of smoking and ovarian cancer

Table 3
Summary of studies that reported ORs for increasing number of lifetime perineal talc applications.

Study	Stratification	Reported Exposure-Response Strata	aOR*	95% CI
Schildkraut et al. (2016) [29]	Lifetime genital powder applications	< 3600 applications, any genital use vs (never use)	1.16	[0.83, 1.63]
		> 3600 applications, any genital use vs (never use)	1.67	[1.23, 2.26]
Whittemore et al. (1988) [31]	Overall trend	Overall trend for 30 uses per month	1.3	[0.88, 1.92]
Wu et al. (2009) [34]	By total times of talc use	≤ 5200 times vs nonuse	1.2	[0.77, 1.88]
		5201 – 15,600 times vs nonuse	1.38	[0.87, 2.20]
		15,601 – 52,000 times vs nonuse	1.34	[0.89, 2.02]
		> 52,000 times	1.99	[1.34, 2.96]
Mills et al. (2004) [24]	By cumulative use (frequency × duration)	First quartile (lowest exposure)	1.03	[0.59, 1.80]
		Second quartile	1.81	[1.10, 2.97]
		Third quartile	1.74	[1.11, 2.73]
		Fourth quartile (highest exposure)	1.06	[0.62, 1.83]
Rosenblatt et al. (2011) [28]	By lifetime number of applications of perineal powder after bathing	1-1,599 applications	1.21	[0.71, 2.06]
		1,600-4,799 applications	2.08	[1.32, 3.27]
		4,800-9,999 applications	0.87	[0.50, 1.53]
		≥10,000 applications	0.87	[0.48, 1.57]
Cramer et al. (2016) [14]	By total genital applications	≤360 total genital applications	1.15	[0.89, 1.47]
		361-1,800 total genital applications	1.36	[1.06, 1.75]
		1,801-7200 total genital applications	1.41	[1.10, 1.80]
		> 7200 total genital applications	1.39	[1.11, 1.75]
Harlow et al. (1992) [19]	Total Lifetime Perineal Applications**	< 1000 applications	1.3	[0.7, 2.7]
		1000 - 10,000 applications	1.5	[0.9, 2.4]
		> 10,000 applications	1.8	[1.0, 3.0]

* aOR: adjusted odds ratio.
** 10,000 applications are equivalent to daily use for 30 year.

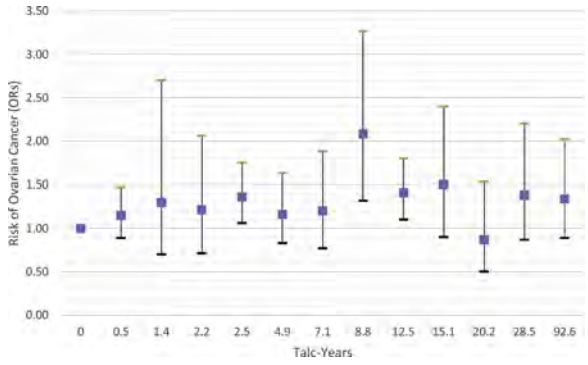


Fig. 3. Ovarian cancer risk estimates at increasing levels of exposure to talc, as reported from multiple studies.

suggest that follow-up periods as long as four decades improve recognition of the carcinogenic effects of smoking [70] longer follow up periods may also improve characterization of the association between talc and ovarian cancer. In this regard, the minimum latency period for radiation-induced ovarian cancer among Hiroshima atomic bomb survivors has been reported to range from 15 to 20 years [71,72]. Common strengths reported in most studies were the selection of population controls in many of the case control studies and having relatively large sample sizes that allowed a multitude of stratified analyses.

Effect estimates in this meta-analysis were pooled from 24 case control studies and 3 cohort studies, and refer to ever vs never use of perineal talc. Pooling by study design showed a notably higher risk estimate for case-control [OR: 1.32 (95% CI: 1.24 to 1.40), P < 0.00001, I^2 = 22%] compared to cohort studies [OR: 1.06 (95% CI: 0.9 to 1.25), P = 0.49, I^2 = 17%]. Although the reasons for this are unclear, the difference could potentially be due to issues relating to latency, study power, or exposure misclassification.

Although cohort study designs are efficient for examining diseases with a long latency period, it is essential that the period between talc exposure and the cancer diagnosis be sufficiently long. Gonzalez et al. [38] suggested that the latency period for ovarian cancer is between 15–20 years. In the cohort studies included in this review,

In addition, cohort studies included may have been underpowered to detect an odds ratio (relative risk) of 1.3 estimated from the case control studies. This was noted by Narod et al. [73], who suggest that cohorts of at least 200,000 women would be needed to reach statistical significance if the true odds ratio is 1.3. The cohort studies included in this review included much smaller cohort sizes, ranging between 41,654 and 78,630 women.

Finally, in cohort studies, talc exposure was assessed at cohort entry and was used as a measure of chronic talc use during follow up. It is possible that women who were not exposed to perineal talc at the time of cohort entry began using talc at a later time, and vice versa, possibly introducing non-differential misclassification of exposure, which could bias the risk estimate towards the null value of unity. Conversely, in the presence of differential exposure misclassification, a bias away from the null hypothesis could accentuate differences between the cohort and case-control studies.

4.1. Exposures and outcomes

All epidemiological studies included in our review evaluated the association between the perineal application of talc and subsequent diagnosis of ovarian cancer. Perineal vs body exposure is an important distinction, as the movement of talc is thought to follow an ascending path from the perineum through the vagina, uterus and fallopian tubes to the ovarian (as well as fallopian tube and peritoneal) epithelium.

Ovarian cancer is a common gynecologic malignancy in developed and developing countries. Risk factors for ovarian cancer include age, infertility, nulligravidity, endometriosis, hereditary ovarian cancer, tobacco and asbestos.

Protective factors for ovarian cancer include oral contraceptives, bilateral tubal ligation, salpingo-oophorectomy, hysterectomy, and breast feeding [74]. It is a difficult cancer to diagnose early, with approximately 60% of the individuals diagnosed after the cancer has metastasized from the pelvic region, where this cancer begins. In the meta-analysis, comparing ovarian cancer risk among women who used talc versus those who never used talc (using both case-control and cohort designs), we observed an approximate 30% increase in ovarian cancer risk in the group who used talc. The most common type of ovarian cancer seen in the general population, and among the women exposed to talc were of epithelial origin, most common histologic type (accounting for about 95% of all cases in the general population), and of serous morphology, the most common subtype (comprising about

75% in the general population).

The cell-type of origin and morphology of talc induced ovarian cancer is similar to that observed in typical ovarian cancer with approximately 95% derived from epithelium (from fallopian tube fimbriae, ovarian or peritoneal) with serous tumors as the most common subtype. Like most ovarian cancers, those associated with talc exposure are typically diagnosed late in the course of the disease (˜60% are diagnosed after the disease has spread outside of the pelvis). This late diagnosis complicates our understanding of the history and origin of the disease.

Demographic factors were analyzed using subgroup analysis where possible, and these were generally consistent with what has been previously observed with respect to ethnicity and risk of ovarian cancer. Additionally, these data also provide support for a mechanism of ovarian cancer induction working via an inflammatory pathway associated with oxidative stress [26,75,76].

A small number of studies explored the issue of ethnicity: Asians (1 study), Hispanics (2 studies), and African-Americans and Whites (3 studies each). Among these studies the risk for talc associated ovarian cancer was 1.70 (Hispanics), 1.67 (African Americans), 1.28 (Whites) and 0.04 (Asians). These risk factors compare with the demographics of ovarian cancer in the US population with an overall prevalence of ovarian cancer of 12.7/100,000 among Whites 13.4/100,00, Hispanics 11.3/100,000, African Americans 9.8/100,000, and Asians 9.8/100,000. The difference in US prevalence and risk of talc induced ovarian cancer among Hispanics and African Americans may provide further evidence concerning exposures or mechanism of action [74].

A variety of factors were assessed with respect to the studies contributing to the meta-analysis, including NOS score for study quality and publication year. In general, the risk of talc associated ovarian cancer was similar among studies with an NOS ≥ 7 or NOS < 7 (maximum is 9). Year of publication also failed to demonstrate a significant impact on reported talc risk estimates.

4.2. Exposure metrics

Given that the epidemiological studies indicate that talc is a possible human carcinogen, we next evaluated the studies to identify those comparing differences in exposure. The initial assessment exploring frequency of use, utilized a qualitative exposure metric: low, medium and high. Ovarian cancer was observed to increase between the medium and high exposure groups, consistent with an exposure-response relationship. Several studies explored duration of use (years) and risk of ovarian cancer; 20+ years (2 studies),10 (5 studies), 10/20 (2 studies), and observed that the risk was greatest in the 20+ year exposure group, followed by lower risk in the 10/20 year and < 10-year exposure groups.

Several studies explored the route of exposure or approach to talc application on ovarian cancer risk, including; hysterectomy, bilateral tubal ligation, diaphragm, underwear, sanitary napkin, as these can provide insight into differences in exposure of the fallopian tube, ovarian and peritoneal epithelium. Use of a diaphragm, as well as tubal ligation act to interrupt exposure of perineal talc to reproductive tract. In contrast, application to underwear and sanitary napkin exposure will provide broader exposures. As hypothesized, the use of diaphragm and bilateral tubal ligation decreased ovarian cancer risk [23].

4.3. Modifying factors

Modifiers of the risk of ovarian cancer, either associated with talc exposure, or a spontaneous disease, can provide clues to potential mechanisms of causation. Menopausal status and use of hormones can modify the risk for ovarian cancer. For example, among post-menopausal women receiving hormonal therapy the risk for ovarian cancer is greater than those who are premenopausal and those who are post-menopausal not receiving hormone therapy. It has also been observed that women receiving fertility treatment who do not become pregnant are at greater risk for ovarian cancer [23]. These data suggest that hormonal status (elevated estrogens and/or gonadotropins) plays a role in the mechanism of action of talc associated ovarian cancer.

Subgroup analyses in the meta-analysis indicated that interruption of the pathway from perineum to pelvis (as with bilateral tubal ligation or use of diaphragm) decreased risk for ovarian cancer. This supports the hypothesis that talc acts locally on the ovary. Evidence from non-human studies suggesting an inflammatory response of epithelial cells to talc, and histological data corroborating those observations, provides additional support for an inflammatory pathway leading to ovarian cancer. One study recently explored the use of anti-inflammatory drugs and observed a decreased risk for ovarian cancer, also supporting an inflammatory pathway due to oxidative stress as a plausible biological mechanism of talc carcinogenicity [75].

4.4. Applying GRADE framework

We applied the GRADE framework [77] to assess the quality of the evidence derived from the studies included this review (Table 4). Using GRADEpro for the assessment, the certainty of the evidence was classified as very low. Several factors are taken into account in the GRADE process. First, we considered our findings from the meta-analysis to lack any serious issues with respect to inconsistency, indirectness, and imprecision. However, we deemed the findings to be subject to an appreciable risk of bias, mainly due to the potential for recall bias in the included case control studies and the relatively short follow-up periods between exposure and outcome assessment in the included cohort

Table 4
GRADE Pro Summary of Findings for Human Studies[a].

Outcomes	Anticipated absolute effects[b] (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with non-use	Risk with perineal use of talc			
Ovarian cancer	64 per 1000	**80 per** 1000 (75 to 85)	**OR 1.28** (1.20 to 1.37)	15,303 cases 199,144 controls (27 observational studies)	VERY LOW[c,d]

[a] **GRADE Working Group grades of evidence are: high certainty (**"We are very confident that the true effect lies close to that of the estimate of the effect."); moderate certainty (We are very confident that the true effect lies close to that of the estimate of the effect.t"); low certainty (Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect."; and very low certainty ("We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.).

[b] The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **OR:** Odds ratio.

[c] Twenty-four studies were case-control studies; recall bias may be an issue given long latency period.

[d] Three studies were cohort studies, and were assessed as having a relatively short follow-up period for the development of ovarian cancer (15–20 years).

studies.

Study design is a critical component in the GRADE assessment, where randomized controlled trials (RCTs) are viewed as providing considerably stronger evidence than observational studies [77]. As such, the evidence derived from the observational studies in this review was initially classified as being of low certainty within the GRADE framework; this was further downgraded to very low certainty in light of the risk of bias noted above. Despite the very low certainty assigned by the GRADE evaluation, which heavily favors evidence from RCTs (a difficult approach to study the potential carcinogenicity of talc following perineal exposure), we maintain our conclusion that talc is a possible cause of human cancer in humans based on the totality of evidence from multiple observational studies and a plausible biological pathway involving chronic inflammation and oxidative stress.

5. Conclusion

We conducted an extensive search, examination, assessment and analysis of evidence from published original human and non-human studies and from published reviews that considered the association between genital/perineal use of talc powder and risk of ovarian cancer. The steps followed in conducting this review are summarized in Fig. 4, along with the key findings at each step. Consistent with a previous evaluation by the IARC in 2010 [2], the present evaluation of all currently available relevant data indicates that perineal exposure to talc powder is a possible cause of ovarian cancer in humans.

While acknowledging the valuable contributions made by previous research groups, our review provides the most up-to-date and comprehensive examination of the association between perineal exposure to talc and ovarian cancer risk, supported by careful examination of data from the original studies and elimination of studies reporting on overlapping populations. It is reassuring that earlier expert reviews, including the two recent systematic reviews [3,5] arrived at compatible conclusions, thereby reinforcing the robustness of the association between perineal exposure to talc and ovarian cancer risk.

Source of funding

This work was supported by Health Canada as part of their Chemicals Management Plan via contract # 4600001163 to Risk Sciences International (RSI), Ottawa, ON, Canada.

Acknowledgments and Declarations

All authors who contributed to both this study and manuscript report no conflict of interest in relation to the planning for and conducting this study as well as the preparation of this manuscript. Although the research project and manuscript preparation were conducted under contract to Health Canada, the views and conclusions presented in this article are those of the authors alone.

D. Krewski is the Natural Sciences and Engineering Council of Canada Chair in Risk Science at the University of Ottawa, and Chief Risk Scientist for Risk Sciences International (RSI), a Canadian company established in 2006 in partnership with the University of Ottawa (www.riskciences.com). Dr. Mohamed Kadry Taher, Dr. Nawal Farhat, and Dr. Donald Mattison report personal fees from RSI in relation to this work. Preliminary versions of this paper were presented at the National Cancer Institute Directors' Meeting held in Lyon, France on July 11-13, 2018, and at the 2018 Canada-China Summit for Perinatal Health held in Guangzhou, China on December 1, 2018, and benefited from comments provided by international experts attending those meetings.

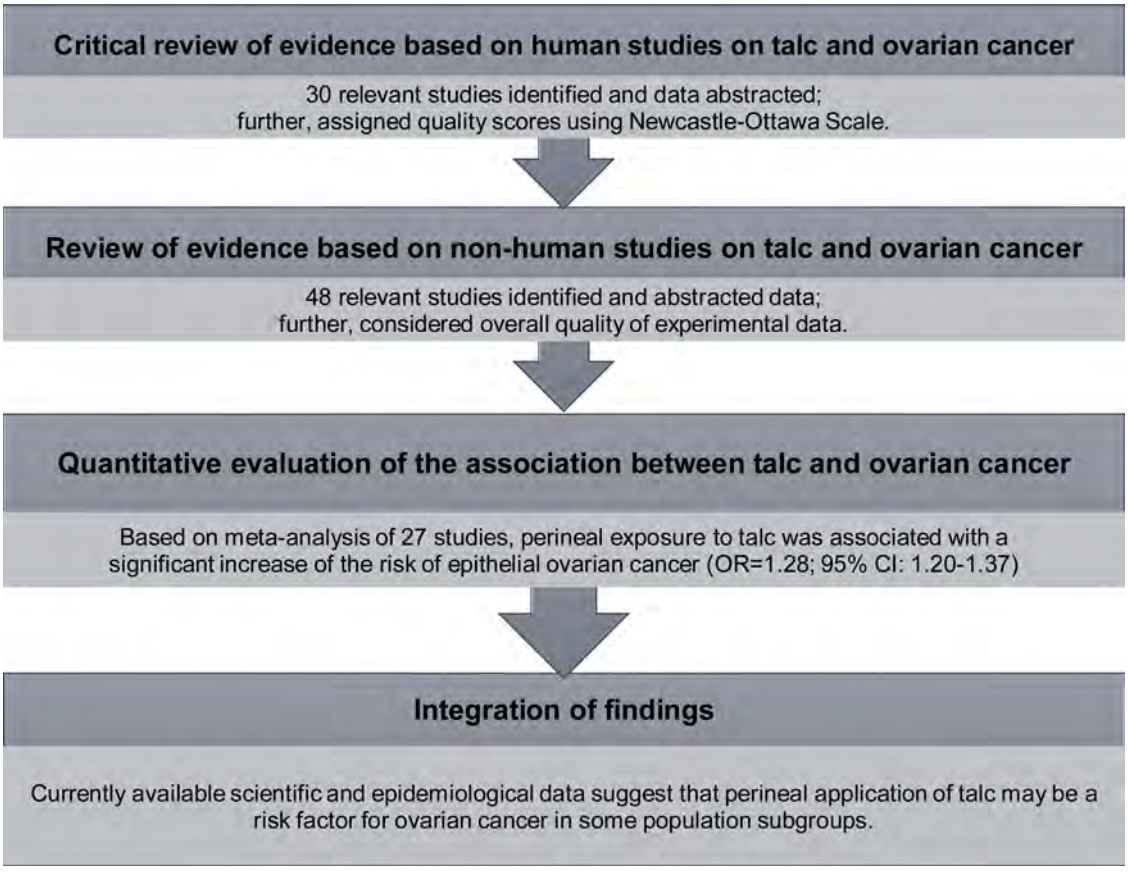


Fig. 4. Detailed process flow for assessment of talc carcinogenecity.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.reprotox.2019.08.015.

References

[1 R. Siegel, J. Ma, Z. Zou, A. Jemal, Cancer statistics, 2014, CA Cancer J. Clin. 64 (1) (2014) 9–29.
[2 IARC/International Agency for Research on Cancer, Carbon black, titanium dioxide, and talc, IARC Monogr. Eval. Carcinog. Risks Hum. 93 (2010) 1–413.
[3 W. Berge, K. Mundt, H. Luu, P. Boffetta, Genital use of talc and risk of ovarian cancer: a meta-analysis, Eur. J. Cancer Prev. (2017).
[4 J. Higgins, S. Green, Cochrane Handbook for Systematic Reviews of Interventions, (2011) www.cochrane-handbook.org.
[5 R. Penninkilampi, G.D. Eslick, Perineal Talc Use and Ovarian Cancer: A Systematic Review and Meta-Analysis, Epidemiology 29 (1) (2018) 41–49.
[6 G. Wells, B. Shea, D. O'Connell, J. Peterson, V. Welch, M. Losos, P. Tugwell, The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses, (2008) (Accessed May 8 2017), http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
[7 M.L. McPheeters, S. Kripalani, N.B. Peterson, R.T. Idowu, R.N. Jerome, S.A. Potter, J.C. Andrews, Closing the quality gap: revisiting the state of the science (vol. 3: quality improvement interventions to address health disparities), Evid. Rep. Assess. 208.3 (2012) 1–475.
[8 M. Hersi, P. Quach, M.-D. Wang, J. Gomes, J. Gaskin, D. Krewski, Systematic reviews of factors associated with the onset and progression of neurological conditions in humans: A methodological overview, NeuroToxicology 61 (Complete) (2017) 12–18.
[9 D. Moher, K.F. Schulz, D.G. Altman, The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials, Clin. Oral Investig. 7 (1) (2003) 2–7.
[10 D.W. Cramer, A.F. Vitonis, K.L. Terry, W.R. Welch, L.J. Titus, The Association Between Talc Use and Ovarian Cancer: A Retrospective Case-Control Study in Two US States, Epidemiology 27 (3) (2016) 334–346.
[11 M.A. Gates, B.A. Rosner, J.L. Hecht, S.S. Tworoger, Risk factors for epithelial ovarian cancer by histologic subtype, Am. J. Epidemiol. 171 (1) (2010) 45–53.
[12 D.M. Gertig, D.J. Hunter, D.W. Cramer, G.A. Colditz, F.E. Speizer, W.C. Willett, S.E. Hankinson, Prospective study of talc use and ovarian cancer, J. Natl. Cancer Inst. 92 (3) (2000) 249–252.
[13 S.C. Houghton, K.W. Reeves, S.E. Hankinson, L. Crawford, D. Lane, J. Wactawski-Wende, C.A. Thomson, J.K. Ockene, S.R. Sturgeon, Perineal powder use and risk of ovarian cancer, J. Natl. Cancer Inst. 106 (9) (2014).
[14 H. Langseth, K. Kjaerheim, Ovarian cancer and occupational exposure among pulp and paper employees in Norway, Scand. J. Work Environ. Health 30 (5) (2004) 356–361.
[15 M. Booth, V. Beral, P. Smith, Risk factors for ovarian cancer: a case-control study, Br. J. Cancer 60 (4) (1989) 592–598.
[16 S. Chang, H.A. Risch, Perineal talc exposure and risk of ovarian carcinoma, Cancer 79 (12) (1997) 2396–2401.
[17 Y. Chen, P.C. Wu, J.H. Lang, W.J. Ge, P. Hartge, L.A. Brinton, Risk factors for epithelial ovarian cancer in Beijing, China, Int. J. Epidemiol. 21 (1) (1992) 23–29.
[18 L.S. Cook, M.L. Kamb, N.S. Weiss, Perineal powder exposure and the risk of ovarian cancer. [Erratum appears in Am J Epidemiol 1998 Aug 15;148(4):410, Am. J. Epidemiol. 145 (5) (1997) 459–465.
[19 D.W. Cramer, W.R. Welch, R.E. Scully, C.A. Wojciechowski, Ovarian cancer and talc: a case-control study, Cancer 50 (2) (1982) 372–376.
[20 M.A. Gates, S.S. Tworoger, K.L. Terry, L. Titus-Ernstoff, B. Rosner, Id. Vivo, D.W. Cramer, S.E. Hankinson, Talc use, variants of the GSTM1, GSTT1, and NAT2 genes, and risk of epithelial ovarian cancer, Cancer Epidemiol. Biomarkers Prev. 17 (9) (2008) 2436–2444.
[21 A. Green, D. Purdie, C. Bain, V. Siskind, P. Russell, M. Quinn, B. Ward, Tubal sterilisation, hysterectomy and decreased risk of ovarian cancer. Survey of Women's Health Study Group, Int. J. Cancer 71 (6) (1997) 948–951.
[22 B.L. Harlow, D.W. Cramer, D.A. Bell, W.R. Welch, Perineal exposure to talc and ovarian cancer risk, Obstet. Gynecol. 80 (1) (1992) 19–26.
[23 M.L. Kurta, K.B. Moysich, J.L. Weissfeld, A.O. Youk, C.H. Bunker, R.P. Edwards, F. Modugno, R.B. Ness, B. Diergaarde, Use of fertility drugs and risk of ovarian cancer: results from a U.S.-based case-control study, Cancer Epidemiol. Biomarkers Prev. 21 (8) (2012) 1282–1292.
[24 M.A. Merritt, A.C. Green, C.M. Nagle, P.M. Webb, S. Australian Cancer, G. Australian Ovarian Cancer Study, Talcum powder, chronic pelvic inflammation and NSAIDs in relation to risk of epithelial ovarian cancer, Int. J. Cancer 122 (1) (2008) 170–176.
[25 P.K. Mills, D.G. Riordan, R.D. Cress, H.A. Young, Perineal talc exposure and epithelial ovarian cancer risk in the Central Valley of California, Int. J. Cancer 112 (3) (2004) 458–464.
[26 R.B. Ness, J.A. Grisso, C. Cottreau, J. Klapper, R. Vergona, J.E. Wheeler, M. Morgan, J.J. Schlesselman, Factors related to inflammation of the ovarian epithelium and risk of ovarian cancer, Epidemiology 11 (2) (2000) 111–117.
[27 K.A. Rosenblatt, M. Szklo, N.B. Rosenshein, Mineral fiber exposure and the development of ovarian cancer, Gynecol. Oncol. 45 (1) (1992) 20–25.
[28 K.A. Rosenblatt, N.S. Weiss, K.L. Cushing-Haugen, K.G. Wicklund, M.A. Rossing, Genital powder exposure and the risk of epithelial ovarian cancer, Cancer Causes Control 22 (5) (2011) 737–742.
[29 J.M. Schildkraut, S.E. Abbott, A.J. Alberg, E.V. Bandera, J.S. Barnholtz-Sloan, M.L. Bondy, M.L. Cote, E. Funkhouser, L.C. Peres, E.S. Peters, A.G. Schwartz, P. Terry, S. Crankshaw, F. Camacho, F. Wang, P.G. Moorman, Association between Body Powder Use and Ovarian Cancer: The African American Cancer Epidemiology Study (AACES)Cancer Epidemiol Biomarkers Prev, Cancer Epidemiol. Biomark. Prev. 25 (10) (2016) 1411–1417.
[30 A.H. Wu, C.L. Pearce, C.C. Tseng, M.C. Pike, African Americans and Hispanics Remain at Lower Risk of Ovarian Cancer Than Non-Hispanic Whites after Considering Nongenetic Risk Factors and Oophorectomy RatesCancer Epidemiol Biomarkers Prev, Cancer Epidemiol. Biomark. Prev. 24 (7) (2015) 1094–1100.
[31 A.H. Wu, C.L. Pearce, C.C. Tseng, C. Templeman, M.C. Pike, Markers of inflammation and risk of ovarian cancer in Los Angeles County, Int. J. Cancer 124 (6) (2009) 1409–1415.
[32 B. Godard, W.D. Foulkes, D. Provencher, J.S. Brunet, P.N. Tonin, A.M. Mes-Masson, S.A. Narod, P. Ghadirian, Risk factors for familial and sporadic ovarian cancer among French Canadians: a case-control study, Am. J. Obstet. Gynecol. 179 (2) (1998) 403–410.
[33 B.L. Harlow, N.S. Weiss, A case-control study of borderline ovarian tumors: the influence of perineal exposure to talc, Am. J. Epidemiol. 130 (2) (1989) 390–394.
[34 P. Hartge, R. Hoover, L.P. Lesher, L. McGowan, Talc and ovarian cancer, JAMA 250 (14) (1983) 1844.
[35 P.G. Moorman, R.T. Palmieri, L. Akushevich, A. Berchuck, J.M. Schildkraut, Ovarian cancer risk factors in African-American and white women, Am. J. Epidemiol. 170 (5) (2009) 598–606.
[36 A. Tzonou, A. Polychronopoulou, C.C. Hsieh, A. Rebelakos, A. Karakatsani, D. Trichopoulos, Hair dyes, analgesics, tranquilizers and perineal talc application as risk factors for ovarian cancer, Int. J. Cancer 55 (3) (1993) 408–410.
[37 C. Wong, R.E. Hempling, M.S. Piver, N. Natarajan, C.J. Mettlin, Perineal talc exposure and subsequent epithelial ovarian cancer: a case-control study, Obstet. Gynecol. 93 (3) (1999) 372–376.
[38 N.L. Gonzalez, K.M. O'Brien, A.A. D'Aloisio, D.P. Sandler, C.R. Weinberg, Douching, Talc Use, and Risk of Ovarian Cancer, Epidemiology 27 (6) (2016) 797–802.
[39 A.S. Whittemore, M.L. Wu, R.S. Paffenbarger Jr, D.L. Sarles, J.B. Kampert, S. Grosser, D.L. Jung, S. Ballon, M. Hendrickson, Personal and environmental characteristics related to epithelial ovarian cancer. II. Exposures to talcum powder, tobacco, alcohol, and coffee, Am. J. Epidemiol. 128 (6) (1988) 1228–1240.
[40 J.C. Wagner, G. Berry, T.J. Cooke, R.J. Hill, F.D. Pooley, J.W. Skidmore, Animal experiments with talc, in: W.H. Walton, B. McGovern (Eds.), Inhaled Particles IV, Part 2, Pergamon Press, Oxford, UK, 1977, pp. 647–654.
[41 A.P. Wehner, T.M. Tanner, R.L. Buschbom, Absorption of ingested talc by hamsters, Food Cosmet. Toxicol. 15 (5) (1977) 453–455.
[42 F. Bischoff, G. Bryson, Independence Mall W., Philadelphia, PATalc at Rodent Intrathoracic, Intraperitoneal, and Subcutaneous Sitse, Proceedings of The American Association for Cancer Research, American Association for Cancer Research Public Ledger Bldg, Suite 816, 150 S191061976, Talc at Rodent Intrathoracic, Intraperitoneal, and Subcutaneous Sitse, Proceedings of The American Association for Cancer Research, American Association for Cancer Research Public Ledger Bldg, Suite 816, 150 S 19106 (1976) pp. 1-1.
[43 J. Jagatic, M.E. Rubnitz, M.C. Godwin, R.W. Weiskopf, Tissue response to intraperitoneal asbestos with preliminary report of acute toxicity of heart-treated asbestos in mice, Environ. Res. 1 (3) (1967) 217–230.
[44 M. Ozesmi, T.E. Patiroglu, G. Hillerdal, C. Ozesmi, Peritoneal mesothelioma and malignant lymphoma in mice caused by fibrous zeolite, Br. J. Ind. Med. 42 (11) (1985) 746–749.
[45 W. Gibel, K. Lohs, K.H. Horn, G.P. Wildner, F. Hoffmann, [Experimental study on cancerogenic activity of asbestos filters (authors transl), Archiv fur Geschwulstforschung 46 (6) (1976) 437–442.
[46 NTP/National Toxicology Program, NTP Toxicology and Carcinogenesis Studies of Talc (CAS No. 14807-96-6)(Non-Asbestiform) in F344/N Rats and B6C3F1 Mice (Inhalation Studies)Natl Toxicol Program Tech Rep Ser, Toxicol. Program Tech. Rep. Ser. (1993) 1–287.
[47 M.M. van den Heuvel, H.J. Smit, S.B. Barbierato, C.E. Havenith, R.H. Beelen, P.E. Postmus, Talc-induced inflammation in the pleural cavity, Eur Respir.J 12 (6) (1998) 1419–1423.
[48 A.R. Buz'Zard, B.H.S. Lau, Pycnogenol® reduces talc-induced neoplastic transformation in human ovarian cell cultures, Phytother. Res. 21 (6) (2007) 579–586.
[49 A.J. Ghio, T.P. Kennedy, A.R. Whorton, A.L. Crumbliss, G.E. Hatch, J.R. Hoidal, Role of surface complexed iron in oxidant generation and lung inflammation induced by silicates, Am. J. Physiol. 263 (5 Pt 1) (1992) L511–8.
[50 A.J. Ghio, J.M. Soukup, L.A. Dailey, J.H. Richards, J.L. Turi, E.N. Pavlisko, V.L. Roggli, Disruption of iron homeostasis in mesothelial cells after talc pleurodesis, Am. J. Respir. Cell Mol. Biol. 46 (1) (2012) 80–86.
[51 N. Nasreen, D.L. Hartman, K.A. Mohammed, V.B. Antony, Talc-induced expression of C-C and C-X-C chemokines and intercellular adhesion molecule-1 in mesothelial cells, Am. J. Respir. Crit. Care Med. 158 (3) (1998) 971–978.
[52 T.C. Hamilton, H. Fox, C.H. Buckley, W.J. Henderson, K. Griffiths, Effects of talc on the rat ovary, Br. J. Exp. Pathol. 65 (1) (1984) 101–106.
[53 M.T. Smith, K.Z. Guyton, C.F. Gibbons, J.M. Fritz, C.J. Portier, I. Rusyn, D.M. DeMarini, J.C. Caldwell, R.J. Kavlock, P.F. Lambert, S.S. Hecht, J.R. Bucher, B.W. Stewart, R.A. Baan, V.J. Cogliano, K. Straif, Key Characteristics of Carcinogens as a Basis for Organizing Data on Mechanisms of CarcinogenesisEnvironmental health perspectives, Environ. Health Perspect. 124 (6) (2016) 713–721.
[54 A. Shukla, M.B. MacPherson, J. Hillegass, M.E. Ramos-Nino, V. Alexeeva, P.M. Vacek, J.P. Bond, H.I. Pass, C. Steele, B.T. Mossman, Alterations in gene expression in human mesothelial cells correlate with mineral pathogenicity, Am. J. Respir. Cell Mol. Biol. 41 (1) (2009) 114–123.
[55 R.B. Ness, C. Cottreau, Possible role of ovarian epithelial inflammation in ovarian

cancer, J. Natl. Cancer Inst. 91 (17) (1999) 1459–1467.
[56 R.E. Scully, Pathology of ovarian cancer precursors, J. Cell. Biochem. Suppl. 23 (1995) 208–218.
[57 A.P. Wehner, R.E. Weller, E.A. Lepel, On talc translocation from the vagina to the oviducts and beyond, Food Chem. Toxicol. 24 (4) (1986) 329–338.
[58 A.P. Wehner, C.L. Wilkerson, W.C. Cannon, R.L. Buschbom, T.M. Tanner, Pulmonary deposition, translocation and clearance of inhaled neutron-activated talc in hamsters, Food Cosmet. Toxicol. 15 (3) (1977) 213–224.
[59 W.J. Henderson, T.C. Hamilton, M.S. Baylis, C.G. Pierrepoint, K. Griffiths, The demonstration of the migration of talc from the vagina and posterior uterus to the ovary in the rat, Environ. Res. 40 (2) (1986) 247–250.
[60 J.C. Phillips, P.J. Young, K. Hardy, S.D. Gangolli, Studies on the absorption and disposition of 3H-labelled talc in the rat, mouse, guinea-pig and rabbit, Food Cosmet.Toxicol 16 (2) (1978) 161–163.
[61 W.J. Henderson, C.A. Joslin, A.C. Turnbull, K. Griffiths, Talc and carcinoma of the ovary and cervix, J. Obstet. Gynaecol. Br. Commonw. 78 (3) (1971) 266–272.
[62 A.N. Rohl, A.M. Langer, I.J. Selikoff, A. Tordini, R. Klimentidis, D.R. Bowes, D.L. Skinner, Consumer talcums and powders: mineral and chemical characterization, J. Toxicol. Environ. Health 2 (2) (1976) 255–284.
[63 USP/United States Pharmacopeia Convention, Talc USP. Revision Bulletin Official: August 1, (2011) Available at: http://www.usp.org/sites/default/files/usp/document/harmonization/excipients/m80360talc.pdf. (Accessed 25 September 2018).
[64 J. Nikitakis, G. McEwen Jr, CTFA compendium of cosmetic ingredient composition: Specifications, CTFA (now known as the Personal Care Products Council), Washington, DC, 1990.
[65 H. Langseth, S.E. Hankinson, J. Siemiatycki, E. Weiderpasse, Perineal use of talc and risk of ovarian cancer, J. Epidemiol. Community Health 62 (4) (2008) 358–360.
[66 M. Huncharek, J.F. Geschwind, B. Kupelnick, Perineal application of cosmetic talc and risk of invasive epithelial ovarian cancer: a meta-analysis of 11,933 subjects from sixteen observational studies, Anticancer Res. 23 (2C) (2003) 1955–1960.
[67 K.L. Terry, S. Karageorgi, Y.B. Shvetsov, M.A. Merritt, G. Lurie, P.J. Thompson, M.E. Carney, R.P. Weber, L. Akushevich, W.H. Lo-Ciganic, K. Cushing-Haugen, W. Sieh, K. Moysich, J.A. Doherty, C.M. Nagle, A. Berchuck, C.L. Pearce, M. Pike, R.B. Ness, P.M. Webb, S. Australian Cancer, G. Australian Ovarian Cancer Study, M.A. Rossing, J. Schildkraut, H. Risch, M.T. Goodman, C. Ovarian Cancer Association, Genital powder use and risk of ovarian cancer: a pooled analysis of 8,525 cases and 9,859 controls, Cancer Prev. Res. 6 (8) (2013) 811–821.
[68 M.S. Rice, M.A. Murphy, S.S. Tworoger, Tubal ligation, hysterectomy and ovarian cancer: a meta-analysis, J. Ovarian Res. 5 (1) (2012) 13.
[69 C.F. Belanger, C.H. Hennekens, B. Rosner, F.E. Speizer, The nurses' health study, Am. J. Nurs. 78 (6) (1978) 1039–1040.
[70 P.D. Terry, A.B. Miller, J.G. Jones, T.E. Rohan, Cigarette smoking and the risk of invasive epithelial ovarian cancer in a prospective cohort study, Eur. J. Cancer (Oxford, England: 1990) 39 (8) (2003) 1157–1164.
[71 S. Tokuoka, K. Kawai, Y. Shimizu, K. Inai, K. Ohe, T. Fujikura, H. Kato, Malignant and benign ovarian neoplasms among atomic bomb survivors, Hiroshima and Nagasaki, 1950-80, J. Natl. Cancer Inst. 79 (1) (1987) 47–57.
[72 K.-H. Tung, L.R. Wilkens, A.H. Wu, K. McDuffie, A.M. Nomura, L.N. Kolonel, K.Y. Terada, M.T. Goodman, Effect of anovulation factors on pre-and post-menopausal ovarian cancer risk: revisiting the incessant ovulation hypothesis, Am. J. Epidemiol. 161 (4) (2005) 321–329.
[73 S.A. Narod, Talc and ovarian cancer, Gynecol. Oncol. 141 (3) (2016) 410–412.
[74 L.-m. Chen, J.S. Berek, Epithelial carcinoma of the ovary, fallopian tube, and peritoneum: epidemiology and risk factors, UpToDate (2014).
[75 W.H. Lo-Ciganic, J.C. Zgibor, C.H. Bunker, K.B. Moysich, R.P. Edwards, R.B. Ness, Aspirin, nonaspirin nonsteroidal anti-inflammatory drugs, or acetaminophen and risk of ovarian cancer, Epidemiology 23 (2) (2012) 311–319.
[76 B. Trabert, L. Pinto, P. Hartge, T. Kemp, A. Black, M.E. Sherman, L.A. Brinton, R.M. Pfeiffer, M.S. Shiels, A.K. Chaturvedi, A. Hildesheim, N. Wentzensen, Pre-diagnostic serum levels of inflammation markers and risk of ovarian cancer in the prostate, lung, colorectal and ovarian cancer (PLCO) screening trial, Gynecol. Oncol. 135 (2) (2014) 297–304.
[77 H. Schünemann, J. Brożek, G. Guyatt, A. Oxman, Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach, (2013) URL: http://gdt.guidelinedevelopment.org/app/handbook/handbook.html [WebCite Cache ID 6psHGGOvH] (2017).

EXHIBIT 10

Perineal Talc Use and Ovarian Cancer

A Systematic Review and Meta-Analysis

Ross Penninkilampi, and Guy D. Eslick

Background: It has been posited that there is an association between perineal talc use and the incidence of ovarian cancer. To date, this has only been explored in observational studies.

Objectives: To perform a meta-analysis to evaluate the association between perineal talc use and risk of ovarian cancer.

Methods: Studies were identified using six electronic databases. Observational studies involving at least 50 cases of ovarian cancer were eligible for inclusion. We analyzed the association between ovarian cancer, including specific types, and any perineal talc use, long-term (>10 years) use, total lifetime applications, and use on diaphragms or sanitary napkins. A subgroup analysis was performed, stratifying by study design and population.

Results: We identified 24 case–control (13,421 cases) and three cohort studies (890 cases, 181,860 person-years). Any perineal talc use was associated with increased risk of ovarian cancer (OR = 1.31; 95% CI = 1.24, 1.39). More than 3600 lifetime applications (OR = 1.42; 95% CI = 1.25, 1.61) were slightly more associated with ovarian cancer than <3600 (OR = 1.32; 95% CI = 1.15, 1.50). An association with ever use of talc was found in case–control studies (OR = 1.35; 95% CI = 1.27, 1.43), but not cohort studies (OR = 1.06; 95% CI = 0.90, 1.25). However, cohort studies found an association between talc use and invasive serous type ovarian cancer (OR = 1.25; 95% CI = 1.01, 1.55). We found an increased risk of serous and endometrioid, but not mucinous or clear cell subtypes.

Conclusions: In general, there is a consistent association between perineal talc use and ovarian cancer. Some variation in the magnitude of the effect was found when considering study design and ovarian cancer subtype.

(*Epidemiology* 2018;29: 41–49)

Submitted July 12, 2017; accepted August 27, 2017.

From the Whiteley-Martin Research Centre, Discipline of Surgery, The University of Sydney, Nepean Hospital, Penrith, NSW, Australia.

This manuscript is original, has not been previously published in whole or in part, and is not under consideration for publication elsewhere. Neither animals nor human subjects were used in this research.

All authors have read the manuscript, agree that the work is ready for submission, and accept the contents of the manuscript.

The authors report no conflicts of interest.

SDC Supplemental digital content is available through direct URL citations in the HTML and PDF versions of this article (www.epidem.com).

Correspondence: Guy D. Eslick, The Whiteley-Martin Research Centre, Discipline of Surgery, The University of Sydney, Nepean Hospital, Level 3, Clinical Building, PO Box 63, Penrith, NSW 2751, Australia. E-mail: guy.eslick@sydney.edu.au.

ISSN: 1044-3983/18/2901-0041
DOI: 10.1097/EDE.0000000000000745

Ovarian cancer is the gynecologic cancer associated with the highest mortality in the United States, in 2012 being the fifth highest cause of cancer death in women with 14,404 deaths in that country.[1] The National Cancer Institute's Surveillance, Epidemiology, and End Results Program (SEER) predicts that in the United States, in 2016, there will be 22,280 incidences of newly diagnosed ovarian cancer, and 14,240 deaths caused by ovarian cancer based on age-adjusted data from 2009 to 2013.[2] The 5-year survival statistics for ovarian cancer are poor, largely because patients usually present with advanced disease, which is less amenable to curative therapy.[3] SEER estimates that only 15% of patients present with disease localized to the ovary, which contributes to a 5-year survival of 46.2%.[2] It is imperative to develop public health programs, which either reduce the incidence of ovarian cancer or detect it at an earlier stage, to reduce the burden of this disease.

Routine pelvic examinations, transvaginal ultrasonography, and tumor markers have been trialed as potential screening tools for ovarian cancer, but are limited in their usefulness. The cancer marker cancer antigen 125 (CA-125, also known as mucin 16) has been found to be elevated in 80% of all ovarian carcinomas, but this falls to 50% in women in which the cancer is localized only to the ovary, where it is most amenable to treatment.[4] As CA-125 has a low sensitivity and limited specificity, it is not recommended as a screening test for women without clinical symptoms.[5] Ultrasound has a reasonable sensitivity but poor specificity and positive predictive value, particularly as it is poor at distinguishing between benign and malignant masses.[6] While the search for an effective screening regimen for ovarian cancer continues, the importance of primary prevention becomes paramount.

Talcum powder is made of talc, a hydrated magnesium silicate, and is used to absorb moisture on the body. Some women choose to dust talc on the perineum, or apply it to diaphragms or sanitary napkins, to reduce friction, keep the skin dry, reduce odor, and prevent rashes. The potential association between perineal talc use and ovarian cancer has been discussed for decades. The first investigation of this association was performed by Cramer et al[7] in 1982, when the investigators found a relative risk of 1.92 (95% CI = 1.27, 2.89) for ovarian cancer when women either dusted the perineum with talc powder or used it on sanitary napkins. Since this time, there has been substantial interest in and research into this association.

In the present context, the association between talc use and ovarian cancer takes on considerable relevance, as the pharmaceutical and consumer products company Johnson & Johnson has recently had damages levied to the total of US$717 million against them in five law suits. In these cases, juries decided that the use of talcum powder caused or contributed to the development of the plaintiff's ovarian cancer. The evidence for the association between perineal talc use and ovarian cancer is based on the body of knowledge from observational studies, and most of these have been retrospective case–control studies prone to recall bias. Hence, while perineal talc use has not been shown to be safe, in a similar regard, a certain causal link between talc use and ovarian cancer has not yet been established.[8,9]

In 2013, a pooled analysis was performed for eight population-based case–control studies, and found a modest increased risk (OR = 1.24) of ovarian carcinoma associated with perineal talc use.[10] In 2007, a meta-analysis was performed of nine observational studies; however, this study only examined the use of talc on contraceptive diaphragms.[11] The overall finding of this meta-analysis was that the use of talc on contraceptive diaphragms was not associated with ovarian cancer. Meta-analyses have been performed on this subject before; however, the most recent was in 2008,[9] and since this time, the results of a number of large case–control studies and two cohort studies[12,13] have been published. Hence, there is a need to update the literature, particularly considering pending litigation against Johnson & Johnson by other claimants, and Johnson & Johnson's potential plans to appeal the previous decisions. Furthermore, producers of talcum powder products continue to sell these products without any warning labels regarding perineal use and potential associations with ovarian cancer. Hence, there is a need for clarification, to allow women to be adequately informed of the risk of use of these products, possibly preventing future harm.

This paper aims to review the literature and provide an overall risk estimate for the association between perineal talc use and ovarian carcinoma. We will also perform subgroup analyses by the method of talc application, the duration of talc use, the total number of perineal talc applications, and the type of ovarian cancer developed to further elucidate the relationship between talc use and ovarian carcinoma.

METHODS

Study Protocol

We followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.[14] R.P. performed a systematic search of the databases MEDLINE (from 1950), PubMed (from 1946), Embase (from 1949), the Cumulative Index to Nursing and Allied Health Literature (CINAHL), LILACS, and the Cochrane Central Register of Controlled Trials through 22 August 2017 to identify relevant articles. The search used the terms ("talc" OR "talcum powder") AND ("ovarian cancer" OR "ovarian carcinoma"), which were searched as text word and as exploded medical subject headings where possible. We also searched the reference lists of relevant articles for appropriate studies. No language restrictions were used in either the search or study selection. We did not search for unpublished literature.

Study Selection

We included studies that met the following inclusion criteria: (1) the study investigated the perineal use of talc in relation to risk of development of ovarian cancer; (2) the study reported adverse events as an odds ratio (OR), or the data were presented such that an OR could be calculated; (3) the 95% confidence interval (CI) was reported, or the data were presented such that the CI could be calculated; and (4) the study involved a minimum of 50 cases. We excluded studies that did not meet the inclusion criteria.

Data Extraction

One of us (R.P.) performed data extraction using a standardized data extraction form, collecting information on the publication year, study design, number of cases, number of controls, total sample size, population type, country, mean age, number of adjusted variables, the risk estimates or data used to calculate the risk estimates, CIs or data used to calculate CIs, and the type of ovarian cancer. R.P. assessed the quality of the studies using the Newcastle-Ottawa Scale (NOS); however, no studies were excluded on the basis of NOS score.[15] Authors were not contacted for missing data. Adjusted ratios were extracted in preference to nonadjusted ratios; however, where ratios were not provided, R.P. calculated unadjusted ORs and CIs.

Statistical Analysis

One of us (G.D.E.) calculated pooled ORs and 95% CIs for the effect of any perineal talc use with all ovarian cancers using a random effects model.[16] Analyses were also performed based on the method of administration (diaphragm, sanitary napkins), duration of use, and type of ovarian cancer developed (all mucinous, mucinous invasive, mucinous borderline, all serous, serous invasive, serous borderline, endometrioid, clear cell). For long-term talc use, we extracted the odds ratio for the group with the longest duration of talc exposure compared with controls, provided that group used talc for a minimum duration of 10 years. For overall lifetime talc applications, groups within each study were divided into either <3600 lifetime applications, equivalent to less than approximately 10 years of daily use, or >3600 applications. Where a group from a study did not completely fit into this dichotomy, we placed it into the category it most closely fit. Details on the categorization of individual groups are available in eTable 1 (http://links.lww.com/EDE/B261). Odds ratios were pooled for invasive serous, invasive mucinous, borderline serous, and borderline mucinous tumors individually. However, as many studies reported only all mucinous or all serous in a single

group, we also ran analyses for risk associated with all mucinous and all serous tumors. Where a study reported separately as borderline and serous, both odds ratios were included separately in the meta-analysis, to ensure all available data were considered.

We tested heterogeneity with Cochran's Q statistic, with $P < 0.10$ indicating heterogeneity, and quantified the degree of heterogeneity using the I^2 statistic, which represents the percentage of the total variability across studies which is due to heterogeneity. I^2 values of 25%, 50%, and 75% corresponded to low, moderate, and high degrees of heterogeneity, respectively.[17] We quantified publication bias using the Egger's regression model,[18] with the effect of bias assessed using the fail-safe number method. The fail-safe number was the number of studies that we would need to have missed for our observed result to be nullified to statistical nonsignificance at the $P < 0.05$ level. Publication bias is generally regarded as a concern if the fail-safe number is less than 5n + 10, with n being the number of studies included in the meta-analysis.[19] All analyses were performed with Comprehensive Meta-analysis (version 3·0; Biostat, Englewood, NJ; 2014).

RESULTS

Study Characteristics

We performed a broad literature search of electronic databases, identifying 363 citations for review (Figure 1). Initially, 318 studies were discarded, with many being narrative reviews, duplicates, animal studies, opinion pieces, editorials, or otherwise irrelevant. Forty-five citations were selected for full-text review. Of these, three were excluded due to being associated with endometrial rather than ovarian cancer, two were meta-analyses, five were duplications of data from the same study, one involved non-perineal application of talc, and seven were otherwise irrelevant. No studies were excluded for failing to report an odds ratio or for not providing the necessary raw data from which an odds ratio could be provided. Some studies provided only the raw data, i.e., the number of cases and controls with and without perineal talc use. This allowed an unadjusted odds ratio to be calculated, which was then included in the analysis. Overall, 27 studies were selected. Note that Wu et al[33] (2015) include results from Wu et al[36] (2009); however, only Wu et al[36] (2009) reported on non-perineal talc use, total lifetime applications, and long-term talc use. Hence data were extracted from Wu et al[33] (2015) for the "any perineal use" outcome, and from Wu et al[36] (2009) for the three other outcomes previously mentioned. Hence, while 27 studies were included in the analysis, only 26 were included in the any perineal use analysis. Three studies were cohort studies, including 890 cases and 181,860 person-years.[12,13,20] The remaining 26 studies were case–control studies, with a total of 13,421 cases and 19,314 controls. The case–control studies are described in eTable 1 (http://links.lww.com/EDE/B261), while the cohort studies are described in eTable 2 (http://links.lww.com/EDE/B261). In total, studies involving 14,311 cases of ovarian cancer were included in this review.

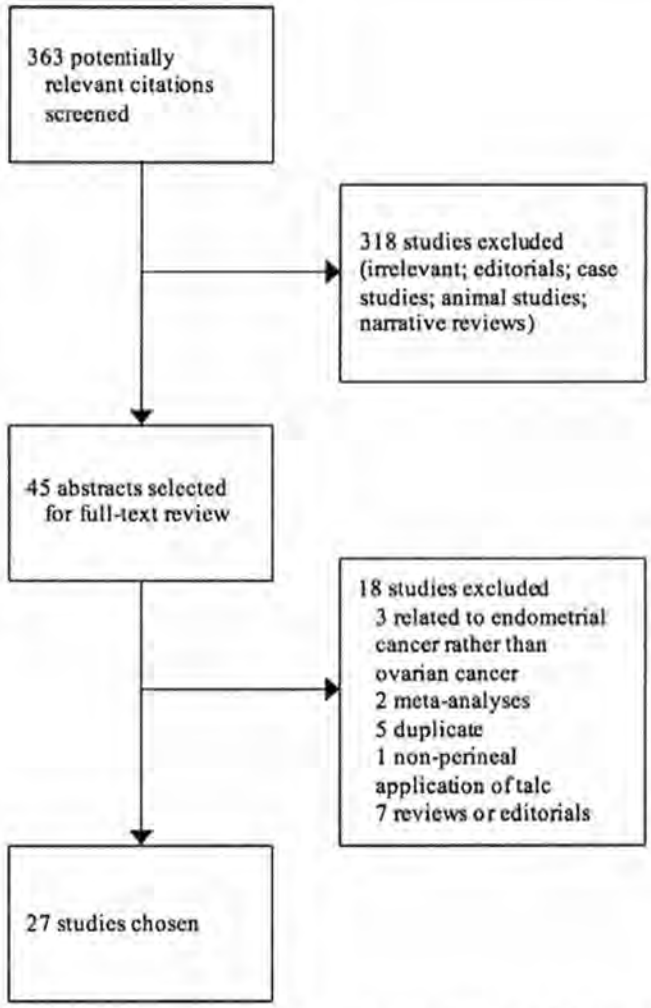


FIGURE 1. PRISMA flowchart for literature search and study selection.

The quality of the studies was assessed using the Newcastle-Ottawa Scale (NOS), which involves separate assessment tools for both case–control and cohort studies.[15] The highest score awarded was 8/10, and the lowest was 5/10. The mean score was 7.0. Almost all studies lost points because the exposure to talc was ascertained through self-report rather than an independently verified source, and because the interviewer was not blinded to cases and controls. Many studies also failed to specifically describe that their chosen controls did not have a personal history of previous ovarian cancer. It may be the case that this was done, but not reported in the study methods. Generally, case ascertainment and matching controls based on age and other factors, often geographical location or ethnicity, were well performed in the reviewed studies. The breakdown of individual study scores is included in Tables 1 and 2. Overall, the quality of studies included in

TABLE 1. Summary of Pooled Effect Sizes for Examined Outcome Variables

	No. Studies	Effect Size	Heterogeneity		Publication Bias
		OR (95% CI)	I^2	*P*	*P*
Method of talc use					
Any perineal	26	1.31 (1.24, 1.39)	10.52	0.31	0.09
Any non-perineal	5	1.24 (1.01, 1.51)	66.84	0.02	0.86
Diaphragm	8	0.84 (0.68, 1.05)	14.76	0.31	0.64
Sanitary napkins	12	1.15 (0.94, 1.41)	43.82	0.05	0.17
Length of talc use					
Long-term use (>10 years)	12	1.25 (1.10, 1.43)	45.11	0.04	0.31
<3600 total applications	5	1.32 (1.15, 1.50)	1.83	0.41	0.20
>3600 total applications	5	1.42 (1.25, 1.61)	12.59	0.33	0.40
Type of ovarian cancer					
All serous	10	1.32 (1.22, 1.43)	0.00	0.75	0.44
Serous invasive	5	1.32 (1.13, 1.54)	25.10	0.25	0.75
Serous borderline	3	1.39 (1.09, 1.78)	0.00	0.94	0.83
All mucinous	9	1.12 (0.94, 1.33)	5.79	0.39	0.79
Mucinous invasive	2	1.34 (0.48, 3.79)	69.39	0.07	NA*
Mucinous borderline	3	1.18 (0.76, 1.81)	34.07	0.22	0.96
Endometrioid	8	1.35 (1.14, 1.60)	0.00	0.61	0.78
Clear cell	3	1.02 (0.75, 1.39)	0.00	0.78	0.22

*NA = not applicable; no publication bias ... result available when there are fewer than three studies in the analysis.

this review was reasonably high. No studies were excluded from the review based on NOS score.

All studies reported at least an odds ratio for any perineal use of talc and its association with ovarian cancer. As previously described, Wu et al[36] (2009) was not included in this analysis to prevent duplication of data. Five studies reported on only non-perineal exposure. Additionally, eight studies provided data for use of talc on a diaphragm, and 12 for sanitary napkins. Twelve studies provided an odds ratio for long-term talc use and its association with ovarian cancer; however, the chosen threshold for long term was variable, from more than 10 years to more than 37.4 years. Five studies reported on the total number of talc applications. It was frequently necessary to report different groups from a single study separately to perform the meta-analysis of this outcome, with the groupings being described specifically in eTable 1 (http://links.lww.com/EDE/B261). Ten studies reported odds ratios for all serous ovarian cancers, five reported for serous invasive cancers, and three reported for serous borderline cancers. Similarly, nine reported for all mucinous cancers, two for mucinous invasive, and three for mucinous borderline. Eight studies reported odds ratios for endometrioid ovarian cancer, and three reported for clear cell ovarian cancer.

Quantitative Data Synthesis

The results of the initial pooling of data from all studies are summarized in Table 1. Pooling of data revealed an increased risk of ovarian cancer associated with any perineal use of talc (Figure 2A; OR = 1.31; 95% CI = 1.24, 1.39). Use of talc long term (>10 years) was also associated with an increased ovarian cancer risk (Figure 2B; OR = 1.25; 95% CI = 1.10, 1.43). Both <3600 total lifetime applications (OR = 1.32; 95% CI = 1.15, 1.50) and >3600 lifetime applications (OR = 1.42; 95% CI = 1.25, 1.61) of talc were associated with an increased risk of ovarian cancer, with a slightly higher risk in the group with greater usage. Talc use on diaphragms or on sanitary napkins was not individually associated with increased risk of ovarian cancer. Any perineal talc use was associated with any serous (Figure 2C; OR = 1.32; 95% CI = 1.22, 1.43), serous invasive (OR = 1.32; 95% CI = 1.13, 1.54), serous borderline (OR = 1.39; 95% CI = 1.09, 1.78), and endometrioid (Figure 2D; OR = 1.35; 95% CI = 1.14, 1.60) subtypes of ovarian cancer, but not the other subtypes.

We performed a subgroup analysis stratifying by study design. It is important to note that there were only three cohort studies, each of which did not report on all the assessed associations. For any perineal talc use, only case–control studies showed an association with ovarian cancer (Figure 2A; OR = 1.35; 95% CI = 1.27, 1.43), while no association was noted for cohort studies (OR = 1.06; 95% CI = 0.90, 1.25). For the other associations assessed, the results are reported in Table 2. In cohort studies, the only association found was between perineal talc use and the incidence of serous invasive cancer subtypes (OR = 1.25; 95% CI = 1.01, 1.55). For borderline serous, borderline mucinous, invasive mucinous, and clear cell ovarian cancer subtypes, no cohort studies provided data for the association and hence the odds ratios reported in eTable 2 (http://links.lww.com/EDE/B261) are derived entirely from case–control studies. The only outcome reported in all three cohort studies was any perineal talc use; hence the available data from prospective studies were limited.

A subgroup analysis related to study population setting, i.e., in the hospital or in the general population, was performed for any perineal talc application. Generally, hospital-based studies were older (pre-2000) than the community-based studies. There were seven hospital-based studies, all of which were case–control studies. There were 20 population-based studies, including 17 case–control studies and all three cohort studies. There was no difference between the pooled results for hospital- and population-based studies (OR = 1.22 vs. 1.33), respectively.

There was heterogeneity in the analysis of non-perineal applications of talc (I^2 = 66.84; P = 0.02). There was no heterogeneity for any of the other outcome measures in either the meta-analysis of all available studies or the subgroup analyses. There was no publication bias in the meta-analysis of any genital talc exposure and ovarian cancer, which included all the studies in the review, except Wu et al[36] (2009) (Figure 3; P = 0.09). The result for publication bias for each of the individual analyses is included in Table 1.

TABLE 2. Summary of Pooled Effect Sizes in Subgroup Analysis by Study Design

	Case–Control Studies (n = 24)				Cohort Studies (n = 3)			
		Effect Size	Heterogeneity			Effect Size	Heterogeneity	
	No. Studies	OR (95% CI)	I^2	*P*	No. Studies	OR (95% CI)	I^2	*P*
Method of talc use								
Any perineal use	23	1.35 (1.27, 1.43)	0.00	0.77	3	1.06 (0.90, 1.25)	18.89	0.29
Non-perineal use	5	1.24 (1.01, 1.51)	66.84	0.02	0	NA	NA	NA
Diaphragm	7	0.81 (0.61, 1.08)	21.92	0.26	1	0.92 (0.68, 1.24)	0.00	1.00
Sanitary napkin	10	1.27 (0.98, 1.65)	40.49	0.09	2	0.93 (0.77, 1.13)	0.00	0.77
Length of talc use								
Long-term use	11	1.29 (1.13, 1.47)	40.53	0.08	1	0.98 (0.75, 1.29)	0.00	1.00
<3600 total applications	5	1.32 (1.15, 1.50)	1.83	0.41	0	NA	NA	NA
>3600 total applications	5	1.42 (1.25, 1.61)	12.59	0.33	0	NA	NA	NA
Type of ovarian cancer								
All serous	12	1.34 (1.23, 1.47)	0.00	0.71	2	1.19 (0.97, 1.47)	0.00	0.61
Serous invasive	3	1.36 (1.05, 1.75)	47.96	0.15	2	1.25 (1.01, 1.55)	0.00	0.33
Serous borderline	3	1.39 (1.09, 1.78)	0.00	0.94	0	NA	NA	NA
All mucinous	9	1.15 (0.93, 1.41)	21.03	0.26	2	0.96 (0.61, 1.53)	0.00	0.84
Mucinous invasive	2	1.34 (0.48, 3.79)	69.39	0.07	0	NA	NA	NA
Mucinous borderline	3	1.18 (0.76, 1.81)	34.07	0.21	0	NA	NA	NA
Endometrioid	6	1.39 (1.16, 1.66)	0.00	0.52	2	1.09 (0.66, 1.80)	0.00	0.48
Clear cell	3	1.02 (0.75, 1.39)	0.00	0.78	0	NA	NA	NA

NA = not applicable; no cohort studies reported on the relevant associations.

DISCUSSION

The present meta-analysis reports a positive association between perineal talc use and ovarian cancer, specifically of the serous and endometrioid histologic subtypes. The mechanism by which perineal talc use may increase the risk of ovarian cancer is uncertain. It has been previously proposed that talc, as a foreign body, may ascend from the vagina through to the uterine tubes and instigate a chronic inflammatory response, which may predispose to the development of ovarian cancer. It is argued that cellular injury, oxidative stress, and local increase in inflammatory mediators such as cytokines and prostaglandins may be mutagenic and hence promote carcinogenesis.[21] In support of this hypothesis, it has been found that hysterectomy or bilateral tubal ligation, in which ovarian exposure to inflammatory mediators would be significantly curtailed, is associated with a reduced risk of ovarian cancer.[22–24] However, the use of non-steroidal anti-inflammatory drugs (NSAIDs) is not inversely associated with the incidence of ovarian cancer, as may be expected if the etiology was related to chronic inflammation.[25,26] It has also been found that human epithelial ovarian cells have an unusually low expression of cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2), which would reduce their sensitivity to the action of NSAIDs.[27] The potential mechanism by which genital talc is associated with an increased risk of ovarian cancer hence remains unclear.

An important finding of this study is that talc use appears to be associated with increased risk of serous ovarian cancer, of both invasive and borderline types, and not with mucinous ovarian cancer. Additionally, endometrioid ovarian cancers but not clear cell cancers were significantly associated with perineal talc use. Intriguingly, a meta-analysis examining the effects of tubal ligation of ovarian cancer risk found a reduced risk of the same subtypes of ovarian cancer as mentioned here: serous and endometrioid, but not mucinous.[24] If chronic inflammation due to ascending foreign bodies is indeed the mechanism by which talc use is associated with increased ovarian cancer risk, then these results fit the picture. The results for non-perineal application of talc were still positive but of lower magnitude, supporting the hypothesis of ascending foreign bodies causing chronic inflammation. It is plausible that non-perineal application of talc may cause increased risk through, e.g., the respiratory tract. Unfortunately, the evidence remains insufficient to understand the mechanism with any reasonable certainty.

We also found a slightly greater increased risk of ovarian cancer with >3600 lifetime applications compared with those with <3600 lifetime applications. The number of lifetime applications is a more valid measure of the patient's exposure to perineal talc than either duration or frequency of use alone. This finding also supports the chronic inflammatory hypothesis, as repeated exposure would induce a longer period of chronic inflammation, and therefore should increase the predisposition to the development of ovarian cancer. It is notable that these data were only available from

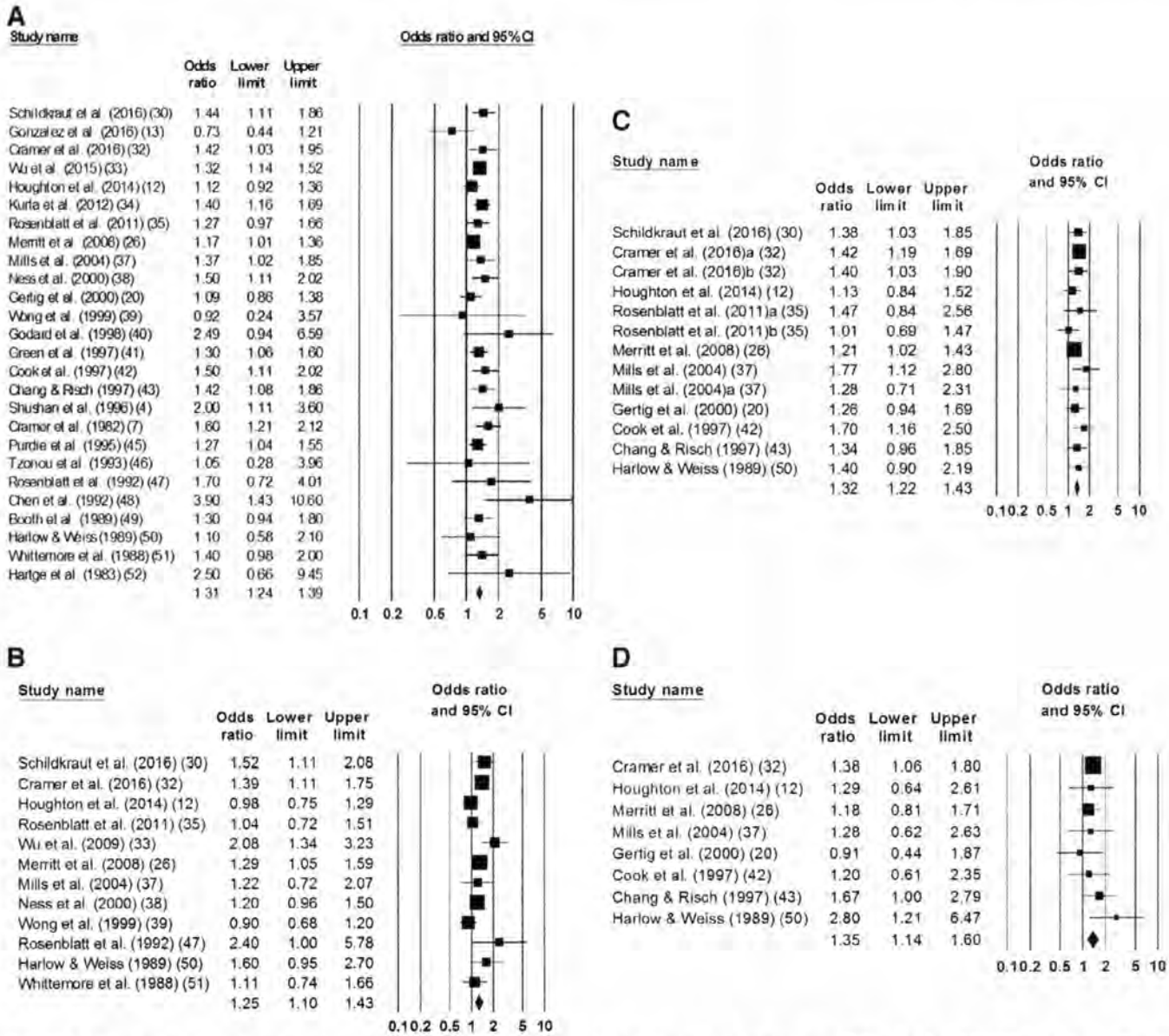


FIGURE 2. A, Any perineal talc use is associated with an increased risk of any ovarian cancer (OR = 1.31; 95% CI = 1.24, 1.39). B, Long-term perineal talc use (>10 years use) is associated with an increased risk of any ovarian cancer, but of a lower magnitude than any perineal use (OR = 1.25; 95% CI = 1.10, 1.43). C, Any perineal talc use is associated with an increased risk of serous ovarian cancers (OR = 1.32; 95% CI = 1.22, 1.43). D, Any perineal talc use is associated with an increased risk of endometrioid type ovarian cancers (OR = 1.35; 95% CI = 1.14, 1.60).

case–control studies, as the three cohort studies did not sufficiently record duration and frequency of use to be included in the analysis. This retrospective finding is therefore prone to recall bias.

This meta-analysis had several strengths. None of the analyses in this review had statistically significant heterogeneity, except for non-perineal application, which indicates consistency in the direction and magnitude of the effect size between individual studies, and strengthening the reliability of the pooled effect sizes. Another strength of this review is the large number of overall cases (n = 14,311), improving the power of the meta-analysis to detect a relatively small effect size, as occurred in this case. Another strength of this review is that the included studies were of relatively high quality as assessed through the NOS, reducing the potential for bias in the conclusions drawn. The NOS revealed that the most common limitations of the included case–control studies were the failure to blind interviewers to case–control status of subjects in the interview, and reliance on memory and self-report for collection of data on perineal talc use.

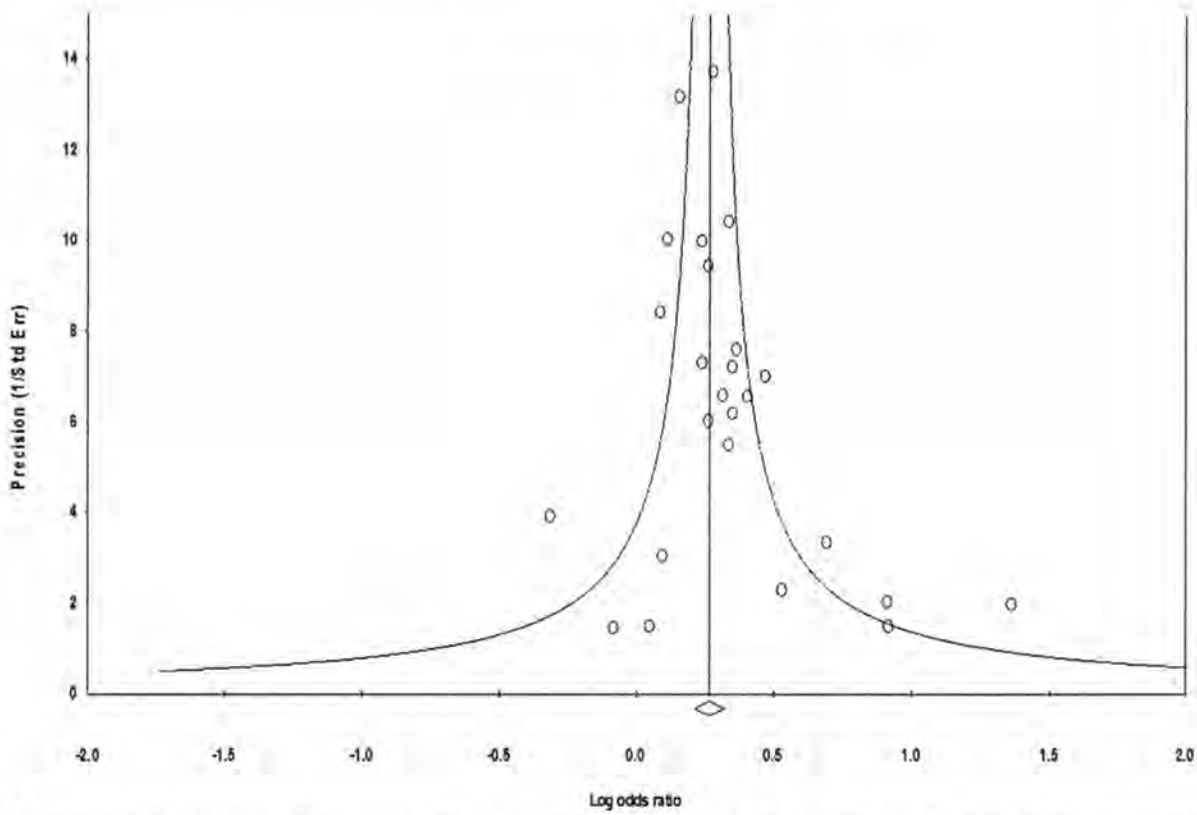


FIGURE 3. Funnel plot for the meta-analysis of studies examining any perineal talc use and risk of ovarian cancer ($P = 0.09$).

A limitation of this study is that it pools nonrandomized studies, primarily case–control studies. The retrospective nature of case–control studies introduces the potential for recall bias. In this case, it is entirely possible that patients with ovarian cancer may be more aware of their previous talc use and hence be more likely to report higher past use. It is possible to attempt to overcome this by blinding the participants to the nature of the study, usually by asking spurious questions; however, the effectiveness of this approach may be limited.[28] Many of the studies in this review recorded data about talc use as part of a more extensive questionnaire focused on other associations, which may reduce the potential for recall bias. However, since the initiation of lawsuits in 2014, there has been extensive media coverage regarding this association, and the potential for recall bias in case–control studies conducted since then may be exacerbated.

Cohort studies are useful in that they are prospective; however, the low incidence of ovarian cancer results in relatively small number of cases even in large cohorts, as seen in the three cohort studies included in this review.[29] Considering potential exposure misclassification issues in case–control studies, the effect for any perineal talc use was very weak in a small number of cohort studies. However, an association between talc use and serous invasive ovarian cancer was found.

Of the studies in this review, case–control studies achieved much large number of cases, in some instances in excess of 2000 cases and a similar number of age-matched controls, which provide greater statistical power for the detection of an effect size of small magnitude. Hence while case–control studies are low-level evidence, they have been preferred in the investigation of the association between talc use and ovarian cancer. They also have the important advantage of not requiring 15 or more years of follow-up, as is necessary for a cohort study to sufficient detect cases of ovarian cancer relative to certain exposures. One potential way to overcome this limitation in future studies is to ensure that talc use is always included in questionnaires of any cohort studies investigating ovarian cancer. It is important not only that talc use be investigated but also the precise location, duration, and frequency of use. As it stands, a meta-analysis of observational studies such as the present study provides the highest level of evidence practically feasible for this research question.

CONCLUSIONS

The results of this review indicate that perineal talc use is associated with a 24%–39% increased risk of ovarian cancer. While the results of case–control studies are prone to recall bias, especially with intense media attention following the commencement of litigation in 2014, the confirmation of an association in cohort studies between perineal talc use and serous invasive ovarian cancer is suggestive of a causal association. Additional epidemiologic evidence from prospective

studies with attention to effects within ovarian cancer subtype is warranted. There is a substantial need for further research on a potential mechanism by which ovarian cancer may be caused by talc, as this will allow a causal relationship to be established or rejected with more certainty. However, particularly because of the dearth of screening tests available for this high-mortality cancer, it is important that research into this association continue as it is a potential avenue for cancer prevention.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin*. 2016;66:7–30.
2. SEER. SEER stat fact sheet: ovary cancer. Accessed 8 May 2016. https://seer.cancer.gov/statfacts/html/ovary.html.
3. Holschneider CH, Berek JS. Ovarian cancer: epidemiology, biology, and prognostic factors. *Semin Surg Oncol*. 2000;19:3–10.
4. Jelovac D, Armstrong DK. Recent progress in the diagnosis and treatment of ovarian cancer. *CA Cancer J Clin*. 2011;61:183–203.
5. Sölétormos G, Duffy MJ, Othman Abu Hassan S, et al. Clinical use of cancer biomarkers in epithelial ovarian cancer: updated guidelines from the European Group on Tumor Markers. *Int J Gynecol Cancer*. 2016;26:43–51.
6. van Nagell JR Jr, Hoff JT. Transvaginal ultrasonography in ovarian cancer screening: current perspectives. *Int J Womens Health*. 2013;6:25–33.
7. Cramer DW, Welch WR, Scully RE, Wojciechowski CA. Ovarian cancer and talc: a case-control study. *Cancer*. 1982;50:372–376.
8. Huncharek M, Muscat J. Perineal talc use and ovarian cancer risk: a case study of scientific standards in environmental epidemiology. *Eur J Cancer Prev*. 2011;20:501–507.
9. Langseth H, Hankinson SE, Siemiatycki J, Weiderpass E. Perineal use of talc and risk of ovarian cancer. *J Epidemiol Community Health*. 2008;62:358–360.
10. Terry KL, Karageorgi S, Shvetsov YB, et al; Australian Cancer Study (Ovarian Cancer); Australian Ovarian Cancer Study Group; Ovarian Cancer Association Consortium. Genital powder use and risk of ovarian cancer: a pooled analysis of 8,525 cases and 9,859 controls. *Cancer Prev Res (Phila)*. 2013;6:811–821.
11. Huncharek M, Muscat J, Onitilo A, Kupelnick B. Use of cosmetic talc on contraceptive diaphragms and risk of ovarian cancer: a meta-analysis of nine observational studies. *Eur J Cancer Prev*. 2007;16:422–429.
12. Houghton SC, Reeves KW, Hankinson SE, et al. Perineal powder use and risk of ovarian cancer. *J Natl Cancer Inst* 2014;106:dju208.
13. Gonzalez NL, O'Brien KM, D'Aloisio AA, Sandler DP, Weinberg CR. Douching, talc use, and risk of ovarian cancer. *Epidemiology*. 2016;27:797–802.
14. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg*. 2010;8:336–341.
15. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised trials in meta-analyses. 2000. Accessed 2 September 2017. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
16. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177–188.
17. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557–560.
18. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315:629–634.
19. Orwin RG. A fail-safe N for effect size in meta-analysis. *J Educ Stat*. 1983;8:157–159.
20. Gertig DM, Hunter DJ, Cramer DW, et al. Prospective study of talc use and ovarian cancer. *J Natl Cancer Inst*. 2000;92:249–252.
21. Ness RB, Cottreau C. Possible role of ovarian epithelial inflammation in ovarian cancer. *J Natl Cancer Inst*. 1999;91:1459–1467.
22. Weiss NS, Harlow BL. Why does hysterectomy without bilateral oophorectomy influence the subsequent incidence of ovarian cancer? *Am J Epidemiol*. 1986;124:856–858.
23. Irwin KL, Weiss NS, Lee NC, Peterson HB. Tubal sterilization, hysterectomy, and the subsequent occurrence of epithelial ovarian cancer. *Am J Epidemiol*. 1991;134:362–369.
24. Cibula D, Widschwendter M, Májek O, Dusek L. Tubal ligation and the risk of ovarian cancer: review and meta-analysis. *Hum Reprod Update*. 2011;17:55–67.
25. Bonovas S, Filioussi K, Sitaras NM. Do nonsteroidal anti-inflammatory drugs affect the risk of developing ovarian cancer? A meta-analysis. *Br J Clin Pharmacol*. 2005;60:194–203.
26. Merritt MA, Green AC, Nagle CM, Webb PM; Australian Cancer Study (Ovarian Cancer); Australian Ovarian Cancer Study Group. Talcum powder, chronic pelvic inflammation and NSAIDs in relation to risk of epithelial ovarian cancer. *Int J Cancer*. 2008;122:170–176.
27. Rodriguez-Burford C, Barnes MN, Oelschlager DK, et al. Effects of nonsteroidal anti-inflammatory agents (NSAIDs) on ovarian carcinoma cell lines: preclinical evaluation of NSAIDs as chemopreventive agents. *Clin Cancer Res*. 2002;8:202–209.
28. Mann CJ. Observational research methods. Research design II: cohort, cross sectional, and case-control studies. *Emerg Med J*. 2003;20:54–60.
29. Narod SA. Talc and ovarian cancer. *Gynecol Oncol*. 2016;141:410–412.
30. Schildkraut JM, Abbott SE, Alberg AJ, et al. Association between body powder use and ovarian cancer: The African American Cancer Epidemiology Study (AACES). *Cancer Epidemiol Biomarkers Prev*. 2016;25:1411–1417.
31. Cramer DW, Xu H. Epidemiologic evidence for uterine growth factors in the pathogenesis of ovarian cancer. *Ann Epidemiol*. 1995;5:310–314.
32. Cramer DW, Vitonis AF, Terry KL, Welch WR, Titus LJ. The association between talc use and ovarian cancer: a retrospective case-control study in two US states. *Epidemiology*. 2016;27:334–346.
33. Wu AH, Pearce CL, Tseng CC, Pike MC. African Americans and Hispanics remain at lower risk of ovarian cancer than non-Hispanic Whites after considering nongenetic risk factors and oophorectomy rates. *Cancer Epidemiol Biomarkers Prev*. 2015;24:1094–1100.
34. Kurta ML, Moysich KB, Weissfeld JL, et al. Use of fertility drugs and risk of ovarian cancer: results from a U.S.-based case-control study. *Cancer Epidemiol Biomarkers Prev*. 2012;21:1282–1292.
35. Rosenblatt KA, Weiss NS, Cushing-Haugen KL, Wicklund KG, Rossing MA. Genital powder exposure and the risk of epithelial ovarian cancer. *Cancer Causes Control*. 2011;22:737–742.
36. Wu AH, Pearce CL, Tseng CC, Templeman C, Pike MC. Markers of inflammation and risk of ovarian cancer in Los Angeles County. *Int J Cancer*. 2009;124:1409–1415.
37. Mills PK, Riordan DG, Cress RD, Young HA. Perineal talc exposure and epithelial ovarian cancer risk in the Central Valley of California. *Int J Cancer*. 2004;112:458–464.
38. Ness RB, Grisso JA, Cottreau C, et al. Factors related to inflammation of the ovarian epithelium and risk of ovarian cancer. *Epidemiology*. 2000;11:111–117.
39. Wong C, Hempling RE, Piver MS, Natarajan N, Mettlin CJ. Perineal talc exposure and subsequent epithelial ovarian cancer: a case-control study. *Obstet Gynecol*. 1999;93:372–376.
40. Godard B, Foulkes WD, Provencher D, et al. Risk factors for familial and sporadic ovarian cancer among French Canadians: a case-control study. *Am J Obstet Gynecol*. 1998;179:403–410.
41. Green A, Purdie D, Bain C, et al. Tubal sterilisation, hysterectomy and decreased risk of ovarian cancer. Survey of Women's Health Study Group. *Int J Cancer*. 1997;71:948–951.
42. Cook LS, Kamb ML, Weiss NS. Perineal powder exposure and the risk of ovarian cancer. *Am J Epidemiol*. 1997;145:459–465.
43. Chang S, Risch HA. Perineal talc exposure and risk of ovarian carcinoma. *Cancer*. 1997;79:2396–2401.
44. Shushan A, Paltiel O, Iscovich J, Elchalal U, Peretz T, Schenker JG. Human menopausal gonadotropin and the risk of epithelial ovarian cancer. *Fertil Steril*. 1996;65:13–18.
45. Purdie D, Green A, Bain C, et al. Reproductive and other factors and risk of epithelial ovarian cancer: an Australian case-control study. Survey of Women's Health Study Group. *Int J Cancer*. 1995;62:678–684.
46. Tzonou A, Polychronopoulou A, Hsieh CC, Rebelakos A, Karakatsani A, Trichopoulos D. Hair dyes, analgesics, tranquilizers and peri-

neal talc application as risk factors for ovarian cancer. *Int J Cancer*. 1993;55:408–410.
47. Rosenblatt KA, Szklo M, Rosenshein NB. Mineral fiber exposure and the development of ovarian cancer. *Gynecol Oncol*. 1992;45:20–25.
48 Chen Y, Wu PC, Lang JH, Ge WJ, Hartge P, Brinton LA. Risk factors for epithelial ovarian cancer in Beijing, China. *Int J Epidemiol*. 1992;21:23–29.
49. Booth M, Beral V, Smith P. Risk factors for ovarian cancer: a case-control study. *Br J Cancer*. 1989;60:592–598.
50. Harlow BL, Weiss NS. A case-control study of borderline ovarian tumors: the influence of perineal exposure to talc. *Am J Epidemiol*. 1989;130:390–394.
51. Whittemore AS, Wu ML, Paffenbarger RS Jr, et al. Personal and environmental characteristics related to epithelial ovarian cancer. II. Exposures to talcum powder, tobacco, alcohol, and coffee. *Am J Epidemiol* 1988;128:1228–1240.
52. Hartge P, Hoover R, Lesher LP, McGowan L. Talc and ovarian cancer. *JAMA*. 1983;250:1844.

Study	Year	Country	Cases (n)	Controls (n)	Mean Age	Participants	Participant Setting	Relevant Outcomes	NOS[a] score
Schildkraut et al. [30]	2016	U.S.	584	745	NR	African-American women aged 20 to 79 with confirmed invasive epithelial ovarian cancer	Population	Any perineal use; non-perineal use; long-term use (>20yr); <3600/>3600 lifetime applications; all serous	8
Cramer et al. [13]	2016	U.S.	2041	2100	NR	Women aged 18-80 with confirmed epithelial ovarian cancer	Population	Any perineal use; non-perineal use; long-term use (>20yr); <3600/>3600 lifetime applications; serous invasive; serous borderline; mucinous borderline; mucinous invasive; endometrioid; clear cell	7
Wu et al. [33]	2015	U.S.	1701	2391	NR	Women aged 18-74 with confirmed epithelial ovarian cancer	Population	Any perineal use	7
Kurta et al. [34]	2012	U.S.	902	1802	NR	Women at least 25yo with confirmed epithelial ovarian cancer, within 9 months of diagnosis	Population	Any perineal use	8
Rosenblatt et al. [35]	2011	U.S.	812	1313	NR	Women aged 35-74 with diagnosed epithelial ovarian cancer	Population	Any perineal use; sanitary napkin; diaphragm; long-term use (>20yr); <3600/>3600 lifetime applications; mucinous borderline; serous borderline; serous invasive	7
Wu et al. [36]	2009	U.S.	609	688	NR	Women aged 18-74 with	Population	Non-perineal use; long-	8

						histologically confirmed epithelial ovarian cancer		term use; <3600/>3600 lifetime applications;	
Merritt et al.[26]	2008	Australia	1576	1509	57.1	Women aged 18-79 with confirmed cases of epithelial ovarian cancer	Population	Any perineal use; long-term use (>25yr); any serous; any mucinous; endometrioid; clear cell	8
Mills et al.[37]	2004	U.S.	256	1122	55.3	Women with confirmed cases of epithelial ovarian cancer	Population	Any perineal use; long-term use (>30yr); serous invasive; serous borderline; mucinous invasive; mucinous borderline; endometrioid; clear cell	8
Ness et al.[38]	2000	U.S.	767	1367	NR	Women aged 20-69 with epithelial ovarian cancer	Population	Any perineal use; non-perineal use; sanitary napkin; diaphragm; long-term use (>10yr)	8
Wong et al.[39]	1999	U.S.	499	755	54.9	Women with primary epithelial ovarian cancer	Hospital	Any perineal use; long-term use (>20yr); sanitary napkin	5
Godard et al.[40]	1998	Canada	170	170	56.3	Women aged 20-84 with histologically confirmed primary ovarian cancer	Population	Any perineal use	6
Green et al.[41]	1997	Australia	824	855	NR	Women aged 18-79 with primary epithelial ovarian cancer	Population	Any perineal use	8
Cook et al.[42]	1997	U.S.	313	422	NR	White women aged 20-79 with epithelial ovarian cancer	Population	Any perineal use; <3600/>3600 lifetime applications; sanitary napkin; diaphragm	6
Chang & Risch[43]	1997	Canada	450	564	57.5	Women aged 35-79 with histologically confirmed primary ovarian cancer	Population	Any perineal use; sanitary napkin; all serous; all mucinous; endometrioid	6

Shushan et al. [4]	1996	Israel	200	408	NR	Women with confirmed epithelial ovarian cancer	Population	Any perineal use	7
Cramer et al. [31]	1995	U.S.	450	454	NR	Women with histologically confirmed epithelial ovarian cancer	Population	Any perineal use	7
Purdie et al. [45]	1995	Australia	824	860	55.1	Women aged 18-79 with histologically confirmed primary ovarian cancer	Population	Any perineal use	8
Tzonou et al. [46]	1993	Greece	189	200	NR	Women <75 who underwent surgery for epithelial ovarian cancer	Hospital	Any perineal use	5
Rosenblatt et al. [47]	1992	U.S.	77	46	NR	Women with newly diagnosed ovarian cancer	Hospital	Any perineal use; diaphragm; sanitary napkin; long-term use (>37.4yrs)	7
Chen et al. [48]	1992	China	112	224	48.8	Women with newly diagnosed ovarian cancer	Population	Any perineal use	8
Booth et al. [49]	1989	U.K.	235	451	51.7	Women aged <65 with histologically diagnosed epithelial ovarian cancer	Hospital	Any perineal use	6
Harlow & Weiss [50]	1989	U.S.	116	158	NR	White women aged 20-79 with mucinous or serous borderline tumours diagnosed in 1980-1985	Population	Any perineal use; diaphragm; sanitary napkin	7
Whittemore et al. [51]	1988	U.S.	188	539	NR	Women aged 18-74 with primary epithelial ovarian cancer	Hospital	Any perineal use; long-term use (>10yrs); diaphragm	8
Hartge et al. [52]	1983	U.S.	135	171	NR	Epithelial ovarian cancer cases in participating hospitals	Hospital	Any perineal use; non-perineal use; diaphragm	6

NR = not reported

[a] Newcastle-Ottawa Quality Assessment Scale, which rates non-randomized studies based on selection, comparability, and exposure. Maximum score of 10.

eTable 1: Study and study participant characteristics for case-control studies.

Study	Year	Country	Included Participants (n)	Cases (n)	Participant Person-Years	Mean Age at Baseline	Participants	Participant Setting	Relevant Outcomes	NOS[a] score
The Sister Study, as reported in Gonzalez et al. (2016) [13]	2016	U.S. and Puerto Rico	41 654	154	NR	54.8	Women aged 35 to 74 years at enrolment each with a full- or half-sister who had been diagnosed with breast cancer	Population	Any perineal use	6
Women's Health Initiative Observational Study, reported in Houghton et al. (2014) [12]	2014	U.S.	61 576	429	757 291	63.3	Postmenopausal women 50 to 79 at the time of enrolment	Population	Any perineal use; long-term use (>10yr); sanitary napkin; diaphragm; serous invasive; any mucinous; endometrioid	7
Nurses' Health Study, reported in Gertig et al. (2000) [20]	2000	U.S.	78 630	307	984 212	NR	Female registered nurses aged 30-55 at enrolment	Population	Any perineal use; sanitary napkin; any serous; serous invasive; endometrioid; any mucinous	6

NR = not reported

[a] Newcastle-Ottawa Quality Assessment Scale, which rates non-randomized studies based on selection, comparability, and exposure. Maximum score of 10.

eTable 2: Study and study participant characteristics for cohort studies.

EXHIBIT 11

JAMA | Original Investigation

Association of Powder Use in the Genital Area With Risk of Ovarian Cancer

Katie M. O'Brien, PhD; Shelley S. Tworoger, PhD; Holly R. Harris, ScD; Garnet L. Anderson, PhD; Clarice R. Weinberg, PhD; Britton Trabert, PhD; Andrew M. Kaunitz, MD; Aimee A. D'Aloisio, PhD; Dale P. Sandler, PhD; Nicolas Wentzensen, MD, PhD

IMPORTANCE The relationship between use of powder in the genital area and ovarian cancer is not established. Positive associations reported in case-control studies have not been confirmed in cohort studies.

OBJECTIVE To estimate the association between use of powder in the genital area and ovarian cancer using prospective observational data.

DESIGN, SETTING, AND PARTICIPANTS Data were pooled from 4 large, US-based cohorts: Nurses' Health Study (enrollment 1976; follow-up 1982-2016; n = 81 869), Nurses' Health Study II (enrollment 1989; follow-up 2013-2017; n = 61 261), Sister Study (enrollment 2003-2009; follow-up 2003-2017; n = 40 647), and Women's Health Initiative Observational Study (enrollment 1993-1998; follow-up 1993-2017; n = 73 267).

EXPOSURES Ever, long-term (≥20 years), and frequent (≥1/week) use of powder in the genital area.

MAIN OUTCOMES AND MEASURES The primary analysis examined the association between ever use of powder in the genital area and self-reported incident ovarian cancer. Covariate-adjusted hazard ratios (HRs) and 95% CIs were estimated using Cox proportional hazards models.

RESULTS The pooled sample included 252 745 women (median age at baseline, 57 years) with 38% self-reporting use of powder in the genital area. Ten percent reported long-term use, and 22% reported frequent use. During a median of 11.2 years of follow-up (3.8 million person-years at risk), 2168 women developed ovarian cancer (58 cases/100 000 person-years). Ovarian cancer incidence was 61 cases/100 000 person-years among ever users and 55 cases/100 000 person-years among never users (estimated risk difference at age 70 years, 0.09% [95% CI, −0.02% to 0.19%]; estimated HR, 1.08 [95% CI, 0.99 to 1.17]). The estimated HR for frequent vs never use was 1.09 (95% CI, 0.97 to 1.23) and for long-term vs never use, the HR was 1.01 (95% CI, 0.82 to 1.25). Subgroup analyses were conducted for 10 variables; the tests for heterogeneity were not statistically significant for any of these comparisons. While the estimated HR for the association between ever use of powder in the genital area and ovarian cancer risk among women with a patent reproductive tract was 1.13 (95% CI, 1.01 to 1.26), the *P* value for interaction comparing women with vs without patent reproductive tracts was .15.

CONCLUSIONS AND RELEVANCE In this analysis of pooled data from women in 4 US cohorts, there was not a statistically significant association between use of powder in the genital area and incident ovarian cancer. However, the study may have been underpowered to identify a small increase in risk.

Editorial page 29

Supplemental content

CME Quiz at jamanetwork.com/learning and CME Questions page 86

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Katie M. O'Brien, Epidemiology Branch, National Institute of Environmental Health Sciences, Research Triangle Park, NC, 27709 (obrienkm2@niehs.nih.gov).

JAMA. 2020;323(1):49-59. doi:10.1001/jama.2019.20079

Some women apply powder to their genitals, either through direct application or on underwear, sanitary napkins, diaphragms or tampons. Most powder products include some mineral talc.[1] Talc was first investigated as a carcinogen based on its relationship to asbestos, which has known carcinogenic effects[2] and may be mined in the same locations. However, all US-based manufacturers of cosmetic talc agreed to ban asbestos in 1976,[3] and the International Agency for Research on Cancer has since concluded there is only "possible" evidence that perineal use of talc-based body powder may be carcinogenic.[1]

This classification was largely based on evidence from observational studies. Case-control studies have reported positive associations between ever use of powder in the genital area and ovarian cancer, with an estimated odds ratio of 1.24 in a pooled analysis[4] and 1.31 in a meta-analysis.[5] However, these findings may be affected by recall bias,[6,7] and a recent surge in talc-related lawsuits and media coverage[8,9] has increased this possibility. Thus, it is crucial to evaluate the talc-ovarian cancer association using prospective data.

To date, 3 large cohort studies have assessed the association between use of powder in the genital area and ovarian cancer risk, with inconsistent results.[10-12] However, ovarian cancer is a rare disease (1.3% lifetime risk in the United States),[13] and individual cohort studies are not sufficiently powered to detect modest associations, particularly if restricted to susceptible subgroups, such as women with patent reproductive tracts (ie, having an intact uterus and no tubal ligation).

To better examine the association between use of powder in the genital area and risk of ovarian cancer, 4 large US cohorts that collected the necessary information were identified: the Nurses' Health Study (NHS), Nurses' Health Study II (NHSII), Sister Study (SIS), and Women's Health Initiative Observational Study (WHI-OS). While associations between genital use of powder and ovarian cancer risk have been reported for 3 of these (NHS, WHI-OS, and SIS),[10-12] the pooled results reported here incorporate updated data, including additional cases and longer follow-up.

Key Points

Question Is use of powder in the genital area associated with the risk of developing ovarian cancer?

Findings In this analysis that pooled data from 4 cohorts with a total of 252 745 women, the hazard ratio for the association between self-reported ever use vs never use of powder in the genital area and incident ovarian cancer was 1.08 (95% CI, 0.99-1.17).

Meaning Among women from 4 prospective cohorts, there was not a statistically significant association between use of powder in the genital area and ovarian cancer, but the study may have been underpowered to identify a small increase in risk.

Methods

Study Sample

The study designs of these 4 US-based cohorts have been described in detail elsewhere.[14-16] Briefly, the NHS (n = 121 700) enrolled registered nurses living in the United States in 1976, and the NHSII (n = 116 429) did the same in 1989. The study protocols were approved by the institutional review boards of the Brigham and Women's Hospital, the Harvard T.H. Chan School of Public Health, and those of participating registries, as required. All participants provided written, informed consent. Although the initial questionnaires did not ask about genital use of powder, participants were queried about powder use on the 1982 NHS and 2013 NHSII questionnaires. We only included follow-up time after the questionnaire about use of powder in the genital area was administered and will refer to the questionnaire that assessed powder use as baseline to maintain consistent language across all 4 studies.

Genital use of powder was assessed at enrollment for SIS between 2003 and 2009 (n = 50 884) and for WHI-OS between 1993 and 1998 (n = 93 676). Women were eligible for SIS if they had a sister previously diagnosed with breast cancer but had no personal diagnosis of breast cancer at enrollment. Eligible participants in WHI-OS were postmenopausal women who resided near one of 40 clinical centers. Both studies were approved by the relevant institutional review boards and all participants provided written, informed consent.

Exposure Assessment

The cohorts differed in how they asked participants about use of powder in the genital area (eAppendix in the Supplement). NHS participants were asked whether they "ever commonly used talcum, baby powder or deodorizing powder" on their "perineal (private) area" (no, <1/week, 1-6 times/week, daily) or on sanitary napkins (yes/no). The NHSII questionnaire asked women to report use only if it occurred at least weekly in the "genital/rectal area or on sanitary napkins, tampons, or underwear" and if so, for how long (<1 year, 1-<10 years, 10-<20 years, 20-<30 years, 30+ years). In SIS, the question specifically focused on use of talcum powder and application to "a sanitary napkin, underwear, diaphragm, or cervical cap, or directly to the vaginal area" in the last year or at the ages of 10 to 13 years. Participants were queried about their frequency of use in the year prior to enrollment (never, <1/mo, 1-3 times/mo, 1-5 times/week, >5 times/week), as well as use during the ages 10-13 (did not use, sometimes, frequently). Women in WHI-OS were asked if they had ever used powder on their "private parts (genital areas)" (yes/no) and for how long they had used it (<1 year, 1-4 years, 5-9 years, 10-19 years, 20+ years), with similar questions for powder use on diaphragms or sanitary pads.

To harmonize across the 4 studies, we defined women as ever vs never users of powder on genital areas. For SIS, ever use included use in the last year or at ages 10 to 13 years. We were also able to examine long-term use, which we defined as use of powder on genitals for at least 20 years (NHSII and WHI-OS) or use at ages 10 to 13 years and also in the last year (SIS). Frequent users were those who reported use of powder in the

genital area at least once per week (NHS, NHSII), at least once per week in the last year, or "frequently" during ages of 10 to 13 years (SIS).

Outcome Assessment

For NHS and NHSII, follow-up questionnaires were distributed every 2 years, at which point participants were asked to report recent cancer diagnoses. Those reporting incident cancers were asked to grant access to their medical records, which were reviewed for confirmation of the diagnosis and disease details. Additional cases were identified from among deceased participants via National Death Index searches. The protocol for SIS was similar, except follow-up questionnaires were collected annually and most participants provided pathology reports rather than complete medical records. Participants in WHI-OS were also asked to self-report cancers on annual questionnaires, but only medically confirmed cases were counted. All 4 studies categorized tumors originating in the ovary, peritoneum, and fallopian tubes as ovarian cancers.

For NHS, NHSII, and SIS, delays in the confirmation process and incomplete retrieval of medical records meant that not all self-reported cases could be medically confirmed. We ran sensitivity analyses limited to medically confirmed cases but included all self-reported diagnoses in our main analyses. Subtype analyses were limited to medically confirmed cases.

Covariates

All 4 studies had substantial covariate data, which we harmonized into a common set of potential confounders or effect modifiers. The following data were included: age at baseline (continuous), race (white, black, other), education (≤high school, some college, completed college), body mass index (BMI [calculated as weight in kilograms divided by height in meters squared], restricted cubic spline), parity (nulliparous, 1 birth, 2 births, ≥3 births), smoking status (never, former, current), oral contraceptive use (ever/never), hormone therapy use (ever/never), tubal ligation status (yes/no), hysterectomy status (yes/no), and menopausal status (premenopausal/postmenopausal). Race was self-reported by the participant, based on provided categories. It was considered to be an important confounder because both ovarian cancer rates[13] and genital powder use vary by race/ethnicity. Only baseline levels of these covariates were considered as confounders, though we did consider post-baseline changes in menopausal status when assessing effect modification.

Statistical Analyses

We used Cox proportional hazards models with age as the primary time scale to estimate hazard ratios (HRs) and 95% CIs measuring the association between genital use of powder and incident ovarian cancer, adjusting for potential confounders. We selected potential confounders using a directed acyclic graph framework,[17] considering covariates that were possibly related to use of powder in the genital area and also ovarian cancer risk.

We excluded women who had ovarian cancer or a bilateral oophorectomy prior to baseline, or who were missing information on powder use or age at ovarian cancer diagnosis. For regression analyses, we additionally excluded women with missing data for 1 or more covariates. Women underwent follow-up from age at baseline until ovarian cancer diagnosis, with censoring at bilateral oophorectomy, end of follow-up, or death from causes other than ovarian cancer. An exception was made for WHI-OS because postbaseline oophorectomy data were not collected. Participants in SIS and WHI-OS who were no longer actively responding to follow-up requests were censored at age of last contact, although their follow-up continued via linkage to the National Death Index.

To better control for differences across studies, we allowed the baseline hazard function to vary across cohorts by implementing study-stratified Cox models. We tested for study heterogeneity by conducting likelihood ratio tests comparing models with and without study × powder interaction terms. For the primary analysis of ever vs never powder use and ovarian cancer risk, we additionally calculated the effect estimate and the *P* value for heterogeneity from a random-effects meta-analysis.[18] Proportional hazards assumptions were tested via likelihood ratio tests of powder × time interaction terms.

Because patency is required for there to be a direct physical pathway between the powder application area and the ovaries, we hypothesized a priori that women with patent reproductive tracts would be more susceptible to the effects of powder use in the genital area on ovarian cancer. We therefore conducted analyses restricted to this subgroup. When estimating the effects of duration of powder use on ovarian cancer risk, we compared long-term (≥20 years) and non-long-term users with never users. Similarly, we compared frequent users (≥1/week) and nonfrequent users with never users. We conducted trend tests using the ordinal forms of these variables.

We also conducted exploratory analyses to examine whether the association between powder use in the genital area and ovarian cancer varied by subgroup. These categorizations were selected based on the existing literature or hypotheses about potential biological mechanisms and included age, race/ethnicity, menopausal hormone therapy use, BMI, and parity. We also considered time-varying menopausal status and follow-up time as effect modifiers and more formally compared subgroups defined by hysterectomy, tubal ligation and patency status. We evaluated heterogeneity across strata of each potential effect modifier by conducting likelihood ratio tests of the interaction between that factor and powder use in the genital area.

For analyses limited to medically confirmed cases of ovarian cancer, we censored unconfirmed cases at their self-reported age of diagnosis. For type-specific analyses, the medically confirmed cases were further divided by invasiveness status (invasive vs borderline), tumor location (epithelial ovarian, peritoneal, or fallopian tube), or histotype (serous, endometroid, mucinous, clear-cell, or other). For an alternative histotype analysis, we defined high-grade

Table 1. Description of Participating Cohorts[a]

	Nurses' Health Study[b]	Nurses' Health Study II[c]	Sister Study[d]	Women's Health Initiative[e]	Total
Sample size	81 869	61 261	40 647	73 267	257 044
Included study period	1982-2016	2013-2017	2003-2017	1993-2017	1982-2017
Follow-up time, median (IQR), y	33.2 (20.0-34.0)	3.8 (3.5-3.9)	9.6 (8.4-11.1)	17.4 (8.7-19.9)	11.2 (3.9-21.0)
Age range at assessment for use of powder in the genital area, y	35-62	48-68	35-77	49-81	35-81
Age, median (IQR), y	48 (42-55)	58 (54-62)	55 (48-61)	63 (57-69)	57 (50-62)
All ovarian cancer cases	1258	76	220	659	2213
Medically confirmed ovarian cancer cases	1055	37	172	659	1923
Powder use in genital area, %					
Ever	41	26	27	53	39
Long-term		6	6	16	10
Frequent	27	26	7		22

Abbreviation: IQR, interquartile range.

[a] More detailed descriptions of the Nurses' Health Study and the Nurses' Health Study II can be found in Bao et al[14]; in Sandler et al[15] for the Sister Study; and in Anderson et al[16] for the Women's Health Initiative.

[b] Powder use in the genital area was assessed in the 1982 follow-up questionnaire, not at study baseline. Participants were excluded if they did not respond to the question regarding use of powder in the genital area (n = 28 584), had ovarian cancer prior to responding to the 1982 questionnaire (n = 174), underwent a bilateral oophorectomy at the time of the 1982 questionnaire (n = 10 896), or did not contribute any person-time after the 1982 questionnaire (n = 4). Frequent use was defined as use of powder in the genital area at least once per week. Women who underwent bilateral oophorectomy during follow-up were censored at age of oophorectomy. Follow-up was complete through June 1, 2016.

[c] Use of powder in the genital area was assessed in the 2013 follow-up questionnaire, not at study baseline. Participants were excluded if they did not respond to the question regarding use of powder in the genital area (n = 41 141), had ovarian cancer prior to 2013 (n = 287), underwent a bilateral oophorectomy at the time of the 2013 questionnaire (n = 13 739), or did not contribute any person-time after the 2013 questionnaire (n = 1). Frequent use was defined as use of powder in the genital area at least once per week. Long-term use was defined as use of powder in the genital area for 20 years or longer. Because data were reported in 2-year cycles, we did not censor for oophorectomy that occurred after 2013. Follow-up was complete through June 1, 2017.

[d] Participants were excluded if they withdrew from the study (n = 2), had ovarian cancer prior to baseline or unclear ovarian cancer status at baseline (n = 225), underwent a bilateral oophorectomy prior to baseline (n = 9009), or did not respond to any of the questions regarding use of powder in the genital area (n = 1001). Ever powder use was defined as use of powder in the genital area during the 12 months prior to baseline or at ages 10 to 13 years. Long-term use was defined as use of powder in the genital area at ages 10 to 13 years and within the last 12 months. Frequent use was defined as use of powder in the genital area at least once per week (during the last 12 months) or *frequently* (as termed in the questionnaire) between ages 10 and 13 years. Women who underwent a bilateral oophorectomy during follow-up were censored at age of oophorectomy. Follow-up was complete through September 15, 2017.

[e] Participants were excluded if they did not complete the questionnaire regarding use of powder in the genital area (n = 342), had ovarian cancer before baseline (n = 641) or unknown cancer status before baseline (n = 890), underwent a bilateral oophorectomy at baseline (n = 18 183), or had no follow-up information (n = 353). Long-term use was defined as use of powder in the genital area for 20 years or longer. Postbaseline oophorectomies were not recorded. Follow-up was complete through February 28, 2017.

serous as grades 2 to 4 serous or grades 3 to 4 endometroid tumors.[19] We estimated the HRs for each set of subtypes using joint Cox proportional hazards models,[20] utilizing likelihood ratio tests to compare model fit for models that did and did not allow the main-effect estimates to differ by subtype. These test results are reported as *P* values for heterogeneity.

In a sensitivity analysis, we attempted to isolate participants who were possibly exposed to asbestos-contaminated talc by limiting analysis to women in WHI-OS and NHS, most of whom were born before 1945. In the age-adjusted and fully adjusted models, we additionally estimated cumulative risk of ovarian cancer by age 70 years and assessed differences in absolute risk among ever vs never users of powder in the genital area using the Breslow method.[21]

Statistical tests were 2-sided, and a *P* value less than .05 was considered statistically significant. Because of the potential for type I error due to multiple comparisons, findings from subgroup and sensitivity analyses should be interpreted as exploratory. All analyses were conducted in SAS 9.4.

Results

After initial exclusions, we had data from 257 044 women, including 2213 who developed incident ovarian cancer (**Table 1**). Use of powder in the genital area was common overall (39%) but varied by cohort with 53% of participants reporting ever use in WHI-OS, 41% in NHS, 27% in SIS, and 26% in NHSII. Long-term use was reported by 16% in WHI-OS and by 6% in both SIS and NHSII; frequent use was reported by 27% in NHS, 26% in NHSII, and 7% in SIS.

After further excluding women with missing covariates (<3% of all participants), 2168 participants with ovarian cancer (1884 medically confirmed) and 250 577 without ovarian cancer remained. Most NHS and WHI-OS participants were born between 1915 and 1944 and most NHSII and SIS participants were born in 1945 or later (eTable 1 in the Supplement), and there appeared to be a generational trend in use of powder in the genital area, with older cohorts more

Table 2. Study-Specific and Pooled Risk Differences, Hazard Ratios, and 95% CIs for the Association Between Ever Use of Powder in the Genital Area and Risk of Ovarian Cancer

Cohort	Person-Years, No. at Risk[a]	No. Without Ovarian Cancer[a]	No. With Ovarian Cancer[a]	Incidence per 100 000 Person-Years[a]	Prevalence of Powder Use in the Genital Area, %[a]		Age-Adjusted RD (95% CI), %[a]	Adjusted RD (95% CI), %[a,b]	Adjusted HR (95% CI)[a,b]
					Without Ovarian Cancer	With Ovarian Cancer			
Ever Used Powder in the Genital Area, All Women									
NHS	2 130 797	79 055	1224	57	41	42	0.06 (−0.07 to 0.20)	0.09 (−0.06 to 0.24)	1.07 (0.95 to 1.20)
NHSII	220 658	60 464	76	34	26	24	−0.10 (−0.44 to 0.24)	−0.15 (−0.49 to 0.20)	0.81 (0.47 to 1.38)
SIS	376 212	40 193	219	58	27	29	0.14 (−0.28 to 0.56)	0.03 (−0.39 to 0.45)	1.02 (0.76 to 1.38)
WHI-OS	1 038 039	70 865	649	63	53	56	0.09 (−0.05 to 0.23)	0.09 (−0.05 to 0.24)	1.11 (0.95 to 1.30)
Pooled estimate[c]	3 765 706	250 577	2168	58	38	44	0.08 (−0.03 to 0.19)	0.09 (−0.02 to 0.19)	1.08 (0.99 to 1.17)[d]
Ever Used Powder in the Genital Area, Women With Patent Reproductive Tracts[e]									
NHS	1 408 991	52 191	850	60	41	44	0.22 (0.03 to 0.40)	0.22 (0.02 to 0.42)	1.16 (1.01 to 1.33)
NHSII	140 534	38 503	51	36	26	27	0.06 (−0.39 to 0.51)	−0.01 (−0.46 to 0.43)	0.98 (0.52 to 1.83)
SIS	226 866	24 080	116	51	25	23	−0.13 (−0.63 to 0.37)	−0.21 (−0.72 to 0.31)	0.84 (0.55 to 1.31)
WHI-OS	614 280	41 928	367	60	51	56	0.12 (−0.08 to 0.32)	0.11 (−0.08 to 0.30)	1.13 (0.92 to 1.39)
Pooled estimate[c]	2 390 672	156 702	1384	58	37	45	0.15 (0.01 to 0.30)	0.15 (0.01 to 0.29)	1.13 (1.01 to 1.26)[f]

Abbreviations: HR, hazard ratio; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II; RD, risk difference; SIS, Sister Study; WHI-OS, Women's Health Initiative Observational Study.

[a] Data are reported among participants with complete covariate information. Includes all self-reported cases.

[b] Referent group is never users. Effect estimates and HRs for women with patency were adjusted for race/ethnicity (white, black, other), education (≤ high school, some college, ≥college graduate), body mass index (calculated as weight in kilograms divided by height in meters squared, [restricted cubic spline]), parity (0, 1, 2, ≥3 births), ever use for oral contraceptives, tubal ligation (yes or no), hysterectomy status (yes or no), menopausal status (premenopausal or postmenopausal), and ever use of hormone therapy. Only effect estimates were adjusted for tubal ligation status (yes or no) and for hysterectomy status (yes or no). All covariates indicate status at time of assessment for use of powder in the genital area. RDs were calculated based on estimated cumulative incidence of ovarian cancer by age 70 years.

[c] Pooled estimates were calculated using Cox proportional hazards models, stratified by study to allow for the baseline hazard functions to vary by cohort, and adjusted for the same covariates as the study-specific models.

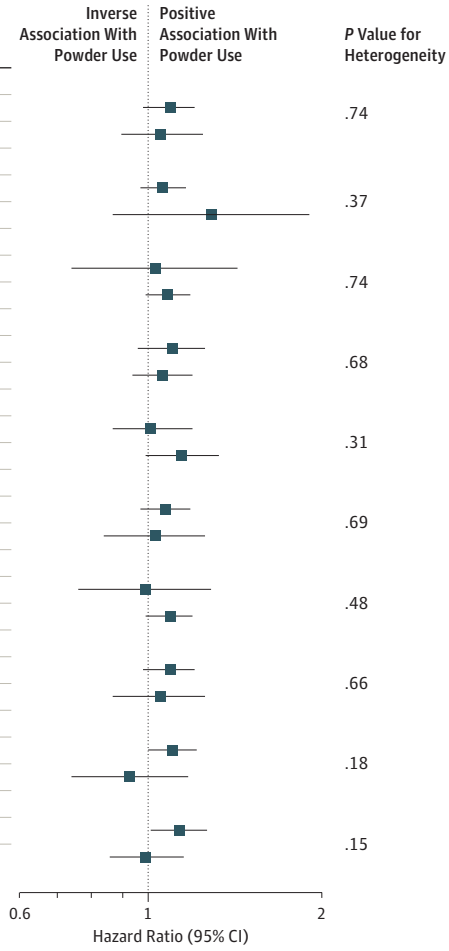
[d] The *P* value for heterogeneity between studies was .81 and was calculated using the likelihood ratio test for study by main-effects interaction term.

[e] Patency indicates having a uterus (ie, no hysterectomy) and no tubal ligation.

[f] The *P* value for heterogeneity between studies was .73 and was calculated using the likelihood ratio test for study by main-effects interaction term.

Figure. Subgroup Analyses for the Association Between Ever Use of Powder in the Genital Area and Risk of Ovarian Cancer, Pooled Hazard Ratios (HRs) and 95% CIs[a]

Characteristic	Participants With Ovarian Cancer, No.[b]	Hazard Ratio (95% CI)	P Value for Heterogeneity
Age, y			
<60	1533	1.09 (0.98-1.20)	.74
≥60	635	1.05 (0.90-1.24)	
Race/ethnicity			
Non-Hispanic white	2061	1.06 (0.97-1.16)	.37
Other	107	1.28 (0.87-1.90)	
Menopause status[c]			
Premenopausal	730	1.03 (0.74-1.42)	.74
Postmenopausal	1438	1.08 (0.99-1.18)	
Follow-up time, y			
0-10	954	1.10 (0.96-1.25)	.68
≥10	1214	1.06 (0.94-1.19)	
Hormone therapy[d]			
Never	654	1.01 (0.87-1.19)	.31
Ever	784	1.14 (0.99-1.32)	
Body mass index[e]			
<30	1757	1.07 (0.97-1.18)	.69
≥30	411	1.03 (0.84-1.25)	
Parity			
Nulliparous	252	0.99 (0.76-1.28)	.48
Parous	1916	1.09 (0.99-1.19)	
Hysterectomy			
No	1658	1.09 (0.98-1.20)	.66
Yes	510	1.05 (0.87-1.25)	
Tubal ligation			
No	1840	1.10 (1.00-1.21)	.18
Yes	328	0.93 (0.74-1.17)	
Patency			
Patent	1384	1.13 (1.01-1.26)	.15
Not patent	784	0.99 (0.86-1.15)	



[a] Adjusted for study, race/ethnicity (white, African American, other), education (<high school, some college, ≥college graduate), body mass index (BMI [calculated as weight in kilograms divided by height in meters squared], restricted cubic spline), parity (0, 1, 2, ≥3 births), ever use of oral contraceptives, tubal ligation (yes or no), hysterectomy (yes or no), menopausal status (premenopausal or postmenopausal), ever hormone therapy use. When estimating HRs within a strata of a variable, that variable was not included in the adjustment set.

[b] Numbers include only participants with complete covariate information.

[c] Effect estimate based on menopausal status updated throughout follow-up. Of the 2168 cases, 165 were diagnosed while the participant was premenopausal and 2003 occurred after menopause.

[d] Among women who were postmenopausal at baseline.

[e] Calculated as weight in kilograms divided by height in meters squared.

likely to report use. Overall, this was a highly educated group (most completed college) and most participants were white (84%-98% of each cohort). Compared with never users, ever users of powder in the genital area were more likely to be black (6% vs 3%; eTable 2 in the Supplement), to be obese (26% vs 19%), or to have had a hysterectomy (22% vs 18%), and less likely to have used oral contraceptives (57% vs 64%).

A total of 2168 women developed ovarian cancer (58 cases per 100 000 person-years; **Table 2**). Consistent with mean age at enrollment, incidence was highest in WHI-OS (63 cases per 100 000 person-years) and lowest in NHSII (34 cases per 100 000 person-years). In the pooled sample, estimated crude cumulative incidence of ovarian cancer at age 70 years was 1.3%, with higher risk among participants in NHS (1.3%) and SIS (1.4%) than in NHSII (0.7%) or WHI-OS (0.9%).

Considering all 4 cohorts, the estimated incidence of ovarian cancer was 61 per 100 000 person-years among ever users and 55 among never users. The estimated adjusted cumulative risk of ovarian cancer by age 70 years among unexposed participants was 1.16%, with an estimated covariate-adjusted risk difference of 0.09% (95% CI, −0.02% to 0.19%) comparing with those who were exposed. The HR for the association between ever powder use and incident ovarian cancer was 1.08 (95% CI, 0.99 to 1.17; Table 2). There was no evidence of heterogeneity across cohorts (*P* value for heterogeneity = .81) and no evidence of a proportional hazards assumption violation (*P* > .99). The estimated HR from the random-effects model was 1.07 (95% CI, 0.98 to 1.17; *P* value for heterogeneity = .71).

When restricted to women with patent reproductive tracts at baseline, the HR was 1.13 (95% CI, 1.01 to 1.26) and the estimated covariate-adjusted risk difference was 0.15% (95% CI, 0.01% to 0.29%). Among women without patent reproductive tracts, the estimated HR was 0.99 (95% CI, 0.86 to 1.15) and the *P* value for heterogeneity comparing the result for women with patency vs without was .15 (**Figure**). The remaining stratified analyses are also presented in the Figure and in eTable 3 in the Supplement.

The covariate-adjusted risk difference for long-term (≥20 years) vs never use was 0.01% (95% CI, −0.21% to 0.24%), and the HR was 1.01 (95% CI, 0.82 to 1.25; *P* value for trend = .57; **Table 3**). The covariate-adjusted risk difference for frequent use (≥1/week) vs none was 0.10% (95% CI, −0.05% to 0.25%), and the HR was 1.09 (95% CI, 0.97 to 1.23; dose-response

Table 3. Study-Specific and Pooled Risk Differences, Hazard Ratios, and 95% CIs for the Association Between Duration and Frequency of Powder Use in the Genital Area and Risk of Ovarian Cancer

Powder Use in the Genital Area	Person-Time at Risk[a]	Noncases[a]	Ovarian Cancer Cases[a]	Incidence per 100 000 Person-Years[a]	Prevalence of Powder Use[a], %		Age-Adjusted RD (95% CI), %[a]	Adjusted RD (95% CI), %[a,b]	Adjusted HR (95% CI)[a,b]	*P* Value for Heterogeneity[c]	*P* Value for Trend[d]
					Noncases	Cases					
All Women											
Long-term use[e]											
NHSII	220 658	60 464	76	34	6	5	−0.11 (−0.71 to 0.49)	−0.18 (−0.77 to 0.41)	0.76 (0.27 to 2.10)		
SIS	376 212	40 193	219	58	6	5	−0.07 (−0.85 to 0.70)	−0.21 (−0.95 to 0.53)	0.85 (0.46 to 1.57)		
WHI-OS	1 034 453	70 598	649	63	16	15	0.04 (−0.16 to 0.24)	0.05 (−0.15 to 0.26)	1.06 (0.85 to 1.34)		
Pooled estimate[f]	1 631 323	171 255	944	58	10	12	0.01 (−0.24 to 0.25)	0.01 (−0.21 to 0.24)	1.01 (0.82 to 1.25)	.90	.49
Used powder ≥1/wk											
NHS	2 130 797	79 055	1224	57	27	29	0.12 (−0.04 to 0.28)	0.14 (−0.04 to 0.31)	1.11 (0.97 to 1.26)		
NHSII	220 658	60 464	76	34	26	24	−0.10 (0.44 to 0.25)	−0.15 (−0.49 to 0.20)	0.81 (0.47 to 1.38)		
SIS	376 212	40 193	219	58	7	9	0.52 (−0.32 to 1.35)	0.35 (−0.46 to 1.15)	1.25 (0.78 to 2.00)		
Pooled estimate[f]	2 727 667	179 712	1519	56	22	26	0.11 (−0.05 to 0.26)	0.10 (−0.05 to 0.25)	1.09 (0.97 to 1.23)	.65	.20
Women With Patent Reproductive Tracts[g]											
Long-term use[e]											
NHSII	140 534	38 503	51	36	6	4	−0.20 (−0.91 to 0.51)	−0.30 (−0.94 to 0.35)	0.59 (0.14 to 2.47)		
SIS	226 866	24 080	116	51	5	5	−0.04 (−1.05 to 0.97)	−0.14 (−1.14 to 0.85)	0.89 (0.39 to 2.05)		
WHI-OS	612 086	41 770	367	60	15	15	0.05 (−0.24 to 0.33)	0.05 (−0.22 to 0.33)	1.06 (0.78 to 1.44)		
Pooled estimate[f]	979 486	104 353	534	54	9	12	0.01 (−0.31 to 0.32)	0.00 (−0.29 to 0.30)	1.00 (0.76 to 1.32)	.81	.66
Used powder ≥1/wk											
NHS	1 408 991	52 191	850	60	27	31	0.28 (0.06 to 0.49)	0.29 (0.05 to 0.52)	1.21 (1.04 to 1.41)		
NHSII	140 534	38 503	51	36	26	27	0.06 (−0.39 to 0.51)	−0.01 (−0.46 to 0.43)	0.98 (0.52 to 1.83)		
SIS	226 866	24 080	116	51	6	8	0.33 (−0.74 to 1.41)	0.20 (−0.84 to 1.25)	1.15 (0.58 to 2.31)		
Pooled estimate[f]	1 776 391	114 774	1017	57	22	28	0.25 (0.04 to 0.46)	0.22 (0.02 to 0.42)	1.19 (1.03 to 1.37)	.69	.03

Abbreviations: HR, hazard ratio; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II; RD, risk difference; SIS, Sister Study; WHI-OS, Women's Health Initiative Observational Study.

[a] Data are reported among participants with complete covariate information. Includes all self-reported cases.

[b] Referent group is never users. Effect estimates are adjusted for race/ethnicity (white, black, other), education (≤high school, some college, ≥college graduate), body mass index (calculated as weight in kilograms divided by height in meters squared, [restricted cubic spline]), parity (0, 1, 2, ≥3 births), ever use of oral contraceptives, tubal ligation (yes or no), hysterectomy status (yes or no), menopausal status (premenopausal or posmenopausal), and ever use of hormone therapy. All covariates indicate status at time of assessment for use of powder in the genital area. RDs were calculated based on estimated cumulative incidence of ovarian cancer by age 70 years.

[c] Likelihood ratio test for study by main-effects interaction term.

[d] A test of the β coefficient for considering frequency (no use, nonfrequent use, frequent use) or duration (no use, non–long-term use, long-term use) of powder as an ordinal variable.

[e] See eAppendix in the Supplement for study-specific definitions of long-term use.

[f] Pooled estimates were calculated using Cox proportional hazard models, stratified by study to allow for the baseline hazard functions to vary by cohort, and adjusted for the same covariates as the study-specific models.

[g] Patency indicates having a uterus (ie, no hysterectomy) and no tubal ligation.

Table 4. Pooled Hazard Ratios and 95% CIs Among Medically Confirmed Cases Overall and by Tumor Invasiveness, Location, and Histotype

	No. of Cases[a]	Hazard Ratio (95% CI)		
		Ever Use[b]	Long-term Use[b]	Frequent Use[b]
All medically-confirmed cases	1884	1.05 (0.96-1.16)	1.03 (0.83-1.28)	1.05 (0.92-1.20)
Invasiveness level				
Invasive only	1538	1.07 (0.97-1.19)	1.08 (0.85-1.37)	1.08 (0.93-1.25)
Borderline	139	1.09 (0.79-1.52)	1.31 (0.59-2.92)	0.98 (0.60-1.60)
P value for heterogeneity[c]		.90	.41	.31
Tumor location				
Epithelial ovarian	1536	1.08 (0.97-1.19)	1.08 (0.85-1.37)	1.09 (0.94-1.27)
Fallopian tube	52	1.19 (0.69-2.08)	2.18 (0.46-10.3)	1.35 (0.69-2.65)
Peritoneal	103	1.12 (0.76-1.65)	1.18 (0.33-4.16)	0.76 (0.44-1.31)
P value for heterogeneity[c]		.92	.58	.02
Histotype				
Serous	1038	1.10 (0.97-1.25)	1.02 (0.75-1.38)	1.07 (0.90-1.28)
Endometroid	157	1.15 (0.83-1.58)	1.14 (0.49-2.63)	1.17 (0.76-1.79)
Mucinous	102	1.03 (0.69-1.54)	1.35 (0.58-3.15)	1.27 (0.73-2.22)
Clear Cell	68	1.17 (0.73-1.89)	1.01 (0.35-2.95)	1.11 (0.55-2.24)
Other	357	0.97 (0.79-1.20)	1.24 (0.79-1.94)	0.93 (0.68-1.27)
P value for heterogeneity[c]		.86	.97	.76
Histotype II[d]				
High-grade serous	732	1.08 (0.93-1.25)	0.99 (0.70-1.40)	1.05 (0.84-1.31)
Low-grade serous	29	1.41 (0.70-2.82)	1.25 (0.17-9.25)	0.70 (0.23-2.09)
Other	601	1.01 (0.86-1.19)	1.19 (0.84-1.69)	1.04 (0.82-1.32)
P value for heterogeneity[c]		.64	.78	.31

[a] Includes ever-use analysis; limited to women with complete covariate information.

[b] Referent group is never users. Adjusted for study, race/ethnicity (white, African-American, other), education (≤high school, some college, ≥college graduate), body mass index (calculated as weight in kilograms divided by height in meters squared, [restricted cubic spline]), parity (0, 1, 2, ≥3 births), ever use of oral contraceptives, tubal ligation (yes or no), hysterectomy status (yes or no), menopausal status (premenopausal or postmenopausal), ever use of hormone therapy.

[c] From competing risks model: likelihood ratio test of model that allows effect estimate to vary by subtype compared with a model that does not.

[d] High-grade serous indicates grades 2 to 4 serous or grades 3 to 4 endometroid; low-grade serous indicates grade 1 serous.

P value for trend =.20). The covariate-adjusted risk difference for the association between frequent powder use and ovarian cancer among women with patent reproductive tracts was 0.22% (95% CI, 0.02% to 0.42%), and the HR was 1.19 (95% CI, 1.03 to 1.37; *P* value for trend = .03).

When the outcome was limited to medically confirmed cases, the HR was attenuated (**Table 4**; HR, 1.05 [95% CI, 0.96 to 1.16] for ever use vs never use). There were no notable differences in estimates by invasive status, tumor location, or histotype. This was also true for analyses limited to women with patent reproductive tracts (eTable 4 in the Supplement). When limited to the older cohorts (NHS and WHI-OS), the estimated pooled HR was 1.09 (95% CI, 0.99 to 1.19) for ever use vs never use. The estimated HR from the young cohorts (NHSII and SIS) was 0.97 (95% CI, 0.75 to 1.26).

Discussion

In this pooled analysis of 4 large US cohorts, there was no statistically significant association between self-reported use of powder in the genital area and risk of ovarian cancer. There were no clear dose-response trends for duration and frequency of powder use in the genital area in relation to ovarian cancer risk. Although the study was underpowered to detect small changes in risk, this is, to our knowledge, the largest study of this topic to date, and it is believed that no other large prospective cohorts have collected data on powder exposure in the genital area.

One of the primary drivers of research on genital use of talc-based products and ovarian cancer has been the potential link between talc and asbestos, which can occur together in nature. In an analysis limited to the older cohorts in which women may have started using powder before the asbestos ban of 1976, the estimated effect remained consistent, with no association observed in the younger cohorts. However, it was recently suggested that some products may have contained asbestos after 1976, meaning that there may not be a clearly defined time period in which talc-based products did or did not contain asbestos.[22] Further, although most cosmetic powder products include some quantity of mineral talc,[1] the percentage varies widely,[23] and exposure to asbestos (through talc) would also depend on the type of product used and the method of application (eg, underwear vs diaphragm).

By irritating epithelial ovarian tissue or fallopian tubes[24] directly, powder could induce an inflammatory response even in the absence of asbestos. This could set off a cascade of increased oxidative stress levels, DNA damage, and cell division, all of which could contribute to carcinogenesis.[25] In this analysis, there was a possible positive association among women with patent reproductive tracts (no history of hysterectomy or tubal ligation), although because the association was not significantly different from that observed in women with nonpatent reproductive tracts, this finding should be considered only exploratory and hypothesis generating. This observation lends support to the hypothesis that powder with or without asbestos could irritate and inflame the reproductive

tract, as patency is required for there to be a direct physical path between the genitals and the fallopian tubes or ovaries.[26] The positive relationships between pelvic inflammatory disease and ovarian cancer[27] and chlamydia infection and ovarian cancer[28] also support an inflammation-mediated mechanism, as does the inverse association between regular aspirin use and ovarian cancer.[29]

One of the main concerns about previous case-control studies on this topic is the possibility for recall bias, which would result if case participants were more likely to report using powder than control participants. As highlighted by Trabert,[7] the African American Cancer Epidemiology Study[6] found evidence supporting this phenomenon. Based on the timing of the first major talc lawsuits,[30] Schildkraut et al[6] stratified their results by year of interview (earlier than 2014 vs 2014 or later), observing that among women interviewed earlier, ever use of powder in the genital area was less-strongly associated with ovarian cancer (odds ratio [OR], 1.19 [95% CI, 0.87 to 1.63]) than among women interviewed later (OR, 2.91 [95% CI, 1.70 to 4.97]). This difference was driven by an increase in the reported prevalence of powder use among case participants (36.5% vs 51.5% of women interviewed early vs later), while self-reported use in the control partcipants remained stable (34.0% vs 34.4%). However, most of the case-control studies that have examined this association recruited well before 2014, and a large pooled analysis published in 2013 reported an OR of 1.24 (95% CI, 1.15 to 1.33).[4] For the current analysis, recall bias was avoided by excluding those with preexisting ovarian cancer.

The strengths of this study were large sample size and long follow-up time. The main analysis included 2168 ovarian cancer cases that developed over 3.8 million person-years. This far exceeds a previous meta-analysis of the published NHS, SIS, and WHI-OS results (890 cases over 182 000 person-years).[5] However, power to investigate links to peritoneal or fallopian tube cancers or histotypes other than serous was still low. Improvements in the classification of tumor types may contribute new insights, especially for fallopian tube cancers, which may be the true point of origin for most serous ovarian cancers.[24] This and other subtype-specific associations should be better examined in the future.

Limitations

This study has several limitations. First, the included cohorts varied widely in how they assessed exposure, particularly the duration and frequency of powder use. There was no evidence of between-study heterogeneity for either the pooled or meta-analysis models of ever use vs never use, but because the 2 largest studies were missing information on duration (NHS) and frequency (WHI-OS) of powder use, the dose-response analyses are underpowered compared with the main results and thus difficult to interpret. Second, use of powder in the genital area could not be assessed as a time-varying factor, as none of the 4 studies collected data on use after baseline.

Third, specific exposure windows could not be examined, nor could type of powder used or patency status at time of powder use. As previously noted, information on powder exposure is typically more limited in cohort studies compared with case-control studies, particularly with respect to dose and duration of use.[31] Therefore, ongoing or future cohort studies should collect detailed information on these topics.

Fourth, as with all observational studies, residual confounding is possible. All 4 included studies recorded detailed information on many potential confounders, which were harmonized across cohorts and adjusted for in multivariable models. However, residual confounding may still be present if the harmonized covariates did not adequately capture the relationship or if any key confounders were missing.

Fifth, the study may have limited generalizability. All 4 cohorts included predominately white, well-educated women, approximately half of whom had a BMI of less than 25, which could raise concerns about generalizability, especially since these factors may be related to powder use. However, these studies have high retention rates and accurate self-reported data, increasing internal validity.

Sixth, confounding by indication is another potential limitation, and it would occur if women with other underlying conditions that were associated with ovarian cancer were also more likely to use powder in the genital area. It is also possible that if powder use is associated with increased risk of other gynecologic conditions (eg, fibroids, ovarian cysts), it can affect whether women receive oophorectomies, hysterectomies, or tubal ligations and alter their risk of developing ovarian cancer. Seventh, because tests to confirm patency were not performed, it is possible that not all women categorized as having a patent reproductive tract in this analysis had truly patent tubes.

Conclusions

In this analysis of pooled data from women in 4 US cohorts, there was not a statistically significant association between self-reported use of powder in the genital area and incident ovarian cancer. However, the study may have been underpowered to identify a small increase in risk.

ARTICLE INFORMATION

Accepted for Publication: November 16, 2019.

Author Affiliations: Epidemiology Branch, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina (O'Brien, Sandler); Department of Cancer Epidemiology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida (Tworoger); Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts (Tworoger); Program in Epidemiology, Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, Washington (Harris); Department of Epidemiology, School of Public Health, University of Washington, Seattle (Harris); Public Health Sciences Division, Fred Hutchinson Cancer Research Center, Seattle, Washington (Anderson); Biostatistics and Computational Biology Branch, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina (Weinberg); Metabolic Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, Maryland (Trabert); Department of Obstetrics and Gynecology, University of Florida College of Medicine-Jacksonville (Kaunitz); Social and

Scientific Systems, Inc, Durham, North Carolina (D'Aloisio); Clinical Genetics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, Maryland (Wentzensen).

Author Contributions: Dr O'Brien had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Joint senior authors: Drs Sandler and Wentzensen.
Concept and design: O'Brien, Tworoger, Sandler, Wentzensen.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: O'Brien, Weinberg, Trabert, Wentzensen.
Critical revision of the manuscript for important intellectual content: O'Brien, Tworoger, Harris, Anderson, Trabert, Kaunitz, D'Aloisio, Sandler, Wentzensen.
Statistical analysis: O'Brien, Tworoger, Harris, Trabert.
Obtained funding: Sandler.
Administrative, technical, or material support: O'Brien, Tworoger, Harris, Kaunitz, D'Aloisio.
Supervision: Sandler, Wentzensen.

Conflict of Interest Disclosures: Dr Tworoger reported receipt of grants from the US Department of Defense Ovarian Cancer Research Program (OCRP) and the National Institutes of Health (NIH) both during the conduct of the study and outside the submitted work. Dr Anderson reported receipt of grants from the National Heart Lung Blood Institute (NHLBI) during the conduct of the study. Dr Kaunitz reported provision of consultancy services to the University of Florida, which receives research funding from companies involved with products related to contraception and treatment of menopausal symptoms; personal fees for consultancy services from Pfizer (injectable contraception), AMAG (treatment of genital atrophy), Mithra (contraceptive and menopausal hormone products), and Merck (implantable and vaginal ring contraception), but no companies involved with sales of powder; royalties from UpToDate; and funding for clinical trials through the University of Florida from Medicines 360 (intrauterine devices), Allergan (treatment of uterine fibroids), Myovant (treatment of uterine fibroids), and Endoceutics (treatment of genital atrophy). No other disclosures were reported.

Funding/Support: This work was supported by the Intramural Research Program of NIH, National Institute of Environmental Health Sciences (Z01-ES044005 to Dr Sandler); the Intramural Research Program of the National Cancer Institute; US Department of Defense OCRP (W81XWH-12-1-0561); NIH (UM1 CA186107, P01 CA87969, UM1 CA176726, and R01 CA67262 [Nurses' Health Study {NHS} and Nurses' Health Study II {NHSII}]); NHLBI, NIH/US Department of Health and Human Services (HHSN268201600018C, HHSN268201600001C, HHSN268201600002C, HHSN268201600003C, and HHSN268201600004C [Women's Health Initiative Observational Study {WHI-OS}]); and the National Institute of Environmental Health Sciences (Sister Study [SIS]). Dr Harris is supported by an NIH grant (K22 CA193860). Statistical analysis services from Westat (Durham, North Carolina) were provided through a support contract from the National Institute of Environmental Health Sciences with Social and Scientific Systems (Durham, North Carolina).

Role of the Funder/Sponsor: None of the sponsors had a role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Information: Statistical analyses were replicated by Westat, an independent contractor (Durham, North Carolina).

Additional Contributions: We would like to thank the participants and staff of the participating cohorts for their valuable contributions as well as the following state cancer registries for their help in the NHS/NHSII: Alabama, Arizona, Arkansas, California, Colorado, Connecticut, Deleware, Florida, Georgia, Idaho, Illinois, Indiana, Iowa, Kentuckyy, Louisiana, Maine, Maryland, Massachusetts, Michigan, Nebraska, New Hampshire, New Jersey, New York, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, Rhode Island, South Carolina, Tennessee, Texas, Virginia, Washington, and Wyoming. The authors acknowledge the Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital, as the home of the NHS and the following investigators from the WHI, from the *NHLBI, Bethesda, Maryland*, Jacques Rossouw, MD, Shari Ludlam, MPH, Joan McGowan, PhD, Leslie Ford, MD, and Nancy Geller, PhD; *Fred Hutchinson Cancer Research Center, Seattle, Washington*, Garnet Anderson, PhD, Ross Prentice, PhD, Andrea LaCroix, PhD, and Charles Kooperberg, PhD; *Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts*, JoAnn E. Manson, MD, DrPH (); *MedStar Health Research Institute/Howard University, Washington, DC*, Barbara V. Howard, PhD; *Stanford Prevention Research Center, Stanford, California*, Marcia L. Stefanick, PhD; *The Ohio State University, Columbus*, Rebecca Jackson, MD; *University of Arizona, Tucson/Phoenix*, Cynthia A. Thomson, PhD, RD; *University at Buffalo, Buffalo, NY*, Jean Wactawski-Wende, PhD; *University of Florida, Gainesville/Jacksonville*, Marian Limacher, MD; *University of Iowa, Iowa City/Davenport*, Jennifer Robinson, MD MPH; *University of Pittsburgh, Pittsburgh, Pennsylvania*, Lewis Kuller, MD, DrPH; *Wake Forest University School of Medicine, Winston-Salem, North Carolina*, Sally Shumaker, PhD, and Mark Espeland, PhD; and *University of Nevada, Reno*, Robert Brunner, PhD. None of aforementioned individuals received compensation for their role in this article.

REFERENCES

1. World Health Organization International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Carbon Black, Titanium Dioxide, and Talc; vol 93; 2010. http://publications.iarc.fr/111 Accessed December 10, 2019.

2. International Agency for Research on Cancer. IARC Monographs: Arsenic, Metals, Fibres, and Dusts; vol 100C; 2012. http://publications.iarc.fr/120 Accessed December 10, 2019.

3. Fiume MM, Boyer I, Bergfeld WF, et al. Safety assessment of talc as used in cosmetics. *Int J Toxicol*. 2015;34(1)(suppl):66S-129S. doi:10.1177/1091581815586797

4. Terry KL, Karageorgi S, Shvetsov YB, et al; Australian Cancer Study (Ovarian Cancer); Australian Ovarian Cancer Study Group; Ovarian Cancer Association Consortium. Genital powder use and risk of ovarian cancer: a pooled analysis of 8525 cases and 9859 controls. *Cancer Prev Res (Phila)*. 2013;6(8):811-821. doi:10.1158/1940-6207.CAPR-13-0037

5. Penninkilampi R, Eslick GD. Perineal talc use and ovarian cancer: a systematic review and meta-analysis. *Epidemiology*. 2018;29(1):41-49. doi:10.1097/EDE.0000000000000745

6. Schildkraut JM, Abbott SE, Alberg AJ, et al. Association between body powder use and ovarian cancer: the African American Cancer Epidemiology Study (AACES). *Cancer Epidemiol Biomarkers Prev*. 2016;25(10):1411-1417. doi:10.1158/1055-9965.EPI-15-1281

7. Trabert B. Body power and ovarian cancer risk—what is the role of recall bias? *Cancer Epidemiol Biomarkers Prev*. 2016;25(10):1369-1370. doi:10.1158/1055-9965.EPI-16-0476

8. Hsu T. Johnson & Johnson told to pay $4.7 billion in baby powder lawsuit. *New York Times*. July 12, 2018. https://www.nytimes.com/2018/07/12/business/johnson-johnson-talcum-powder.html. Accessed December 10, 2019.

9. McGinley L. Does talcum powder cause ovarian cancer? *Washington Post*. August 23, 2017. https://www.washingtonpost.com/news/to-your-health/wp/2017/08/23/does-talcum-powder-cause-ovarian-cancer-experts-are-divided/?utm_term=.9342d83c278f. Accessed December 10, 2019.

10. Gertig DM, Hunter DJ, Cramer DW, et al. Prospective study of talc use and ovarian cancer. *J Natl Cancer Inst*. 2000;92(3):249-252. doi:10.1093/jnci/92.3.249

11. Houghton SC, Reeves KW, Hankinson SE, et al. Perineal powder use and risk of ovarian cancer. *J Natl Cancer Inst*. 2014;106(9):dju208. doi:10.1093/jnci/dju208

12. Gonzalez NL, O'Brien KM, D'Aloisio AA, Sandler DP, Weinberg CR. Douching, talc use, and risk of ovarian cancer. *Epidemiology*. 2016;27(6):797-802. doi:10.1097/EDE.0000000000000528

13. National Cancer Institute Surveillance, Epidemiology, and End Results Program. Cancer stat facts: ovarian cancer. https://seer.cancer.gov/statfacts/html/ovary.html. Accessed December 10, 2019.

14. Bao Y, Bertoia ML, Lenart EB, et al. Origin, methods, and evolution of the three nurses' health studies. *Am J Public Health*. 2016;106(9):1573-1581. doi:10.2105/AJPH.2016.303338

15. Sandler DP, Hodgson ME, Deming-Halverson SL, et al; Sister Study Research Team. The Sister Study: baseline methods and participant characteristics. *Environ Health Perspect*. 2017;125(12):127003. doi:10.1289/EHP1923

16. Anderson GL, Cummings SR, Freedman LS, et al; The Women's Health Initiative Study Group. Design of the Women's Health Initiative clinical trial and observational study. *Control Clin Trials*. 1998;19(1):61-109. doi:10.1016/S0197-2456(97)00078-0

17. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. *Epidemiology*. 1999;10(1):37-48. doi:10.1097/00001648-199901000-00008

18. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7(3):177-188. doi:10.1016/0197-2456(86)90046-2

19. Peres LC, Cushing-Haugen KL, Kobel M, et al Invasive epithelial ovarian cancer survival by histotype and disease stage. *J Natl Cancer Inst*. 2019;111(1):60-68. doi:10.1093/jnci/djy071

20. Xue X, Kim MY, Gaudet MM, et al. A comparison of the polytomous logistic regression and joint cox proportional hazards models for evaluating multiple disease subtypes in prospective cohort studies. *Cancer Epidemiol Biomarkers Prev*. 2013;22(2):275-285. doi:10.1158/1055-9965.EPI-12-1050

21. Breslow NE. Discussion of professor Cox's paper. *J R Stat Soc Ser A (Statistics Soc)*. 1972;34:216. doi:10.1111/j.2517-6161.1972.tb00900.x

22. Rabin RC, Hsu T. Johnson & Johnson feared baby powder's possible asbestos link for years. *New York Times*. December 14, 2018. https://www.nytimes.com/2018/12/14/business/baby-powder-asbestos-johnson-johnson.html. Accessed December 10, 2019.

23. Zazenski R, Ashton WH, Briggs D, et al. Talc: occurrence, characterization, and consumer applications. *Regul Toxicol Pharmacol*. 1995;21(2):218-229. doi:10.1006/rtph.1995.1032

24. Erickson BK, Conner MG, Landen CN Jr. The role of the fallopian tube in the origin of ovarian cancer. *Am J Obstet Gynecol*. 2013;209(5):409-414. doi:10.1016/j.ajog.2013.04.019

25. Ness RB, Cottreau C. Possible role of ovarian epithelial inflammation in ovarian cancer. *J Natl Cancer Inst*. 1999;91(17):1459-1467. doi:10.1093/jnci/91.17.1459

26. Henderson WJ, Joslin CA, Turnbull AC, Griffiths K. Talc and carcinoma of the ovary and cervix. *J Obstet Gynaecol Br Commonw*. 1971;78(3):266-272. doi:10.1111/j.1471-0528.1971.tb00267.x

27. Rasmussen CB, Jensen A, Albieri V, Andersen KK, Kjaer SK. Is pelvic inflammatory disease a risk factor for ovarian cancer? *Cancer Epidemiol Biomarkers Prev*. 2017;26(1):104-109. doi:10.1158/1055-9965.EPI-16-0459

28. Trabert B, Waterboer T, Idahl A, et al. Antibodies against chlamydia trachomatis and ovarian cancer risk in two independent populations. *J Natl Cancer Inst*. 2019;111(2):129-136. doi:10.1093/jnci/djy084

29. Trabert B, Poole EM, White E, et al. Analgesic use and ovarian cancer risk: an analysis in the Ovarian Cancer Cohort Consortium. *J Natl Cancer Inst*. 2019;111(2):137-145. doi:10.1093/jnci/djy100

30. Hsu T. Risk on all sides as 4800 women sue over Johnson's baby powder and cancer. *New York Times*. September 28, 2017. https://www.nytimes.com/2017/09/28/business/johnson-and-johnson-baby-talcum-powder-lawsuits.html. Published Accessed December 10, 2019.

31. Wentzensen N, Wacholder S. Talc use and ovarian cancer: epidemiology between a rock and a hard place. *J Natl Cancer Inst*. 2014;106(9):9-10. doi:10.1093/jnci/dju260

EXHIBIT 12

Published OnlineFirst August 27, 2019; DOI: 10.1158/1055-9965.EPI-19-0375

Research Article

Cancer Epidemiology, Biomarkers & Prevention

Douching, Talc Use, and Risk for Ovarian Cancer and Conditions Related to Genital Tract Inflammation

Iwona M. Gabriel[1], Allison F. Vitonis[1], William R. Welch[2], Linda Titus[3], and Daniel W. Cramer[1]

Abstract

Background: Douching is associated with disorders involving genital tract inflammation and genital talc use with epithelial ovarian cancer (EOC), but their joint effects are infrequently considered.

Methods: From 2,040 cases of EOC and 2,100 controls enrolled in eastern Massachusetts and New Hampshire, we used unconditional logistic regression to estimate risk for EOC associated with douching and/or talc use. In subsets of cases and controls, we also collected information about pelvic inflammatory disease (PID), ectopic pregnancy, and cervical neoplasia to estimate risk for these events from douching and/or talc use.

Results: The adjusted OR and 95% confidence interval (CI) for all EOC was 0.94 (0.76–1.16) in women who douched but never used talc and 1.28 (1.09–1.51) in women who used talc but never douched. Compared with women who never regularly douched or used talc, ORs (95% CIs) were 0.83 (0.52–1.33) for women who both used talc and homemade douches and 1.53 (1.11–2.10) for women who both used talc and store-bought douches. Cases who both douched and used talc were more likely to have had PID compared with cases who had used neither [OR = 5.03 (95% CI, 1.61–15.7)].

Conclusions: Douching is not an independent risk factor for ovarian cancer, but the combination of talc use and store-bought douches may modestly increase the risk for EOC beyond that for talc use alone.

Impact: The joint effect of talc use and douching, especially with commercial products, should be considered in evaluating risks associated with disorders involving genital tract inflammation or EOC.

Introduction

Two relatively common feminine hygienic practices include vaginal douching and use of talc powders or sprays in the genital area. From a National Survey of U.S. women of reproductive age conducted in the late 1980s (1), 37% reported regular douching. A nearly identical proportion reported using talc in their genital area from a survey of older women conducted in the Northwest around the same time period (2). Reasons reported by women who douche include the desire for cleanliness and fresh smell (3), with use often around the time of menses or sexual activity. Because women who douche are also more likely to use talc, the latter group may have similar motivations (2). Epidemiologic factors associated with both practices include Black ethnicity, high body mass index (BMI), married status, and smoking (2, 3).

That a substantial proportion of women in the United States douche or use talc suggests these practices are widely perceived to be innocuous. However, epidemiologic studies suggest both may adversely affect reproductive health. Douching has been associated with pelvic inflammatory disease, ectopic pregnancy, cervical neoplasia, and bacterial and fungal vaginosis (4–9), and genital use of talc has been associated with increased risk of ovarian cancer (10). A recent study suggested that douching may also be associated with ovarian cancer (11); but whether talc use is associated with other adverse reproductive events, like pelvic inflammatory disease (PID) or cervical neoplasia linked to douching, has not been systematically investigated. A key issue in these studies is to what extent the factors that predispose women to douche or use talc use may also be independent risk factors for ovarian cancer or other adverse reproductive events, that is, how well has confounding been controlled for in the studies?

Here, we use data from a large case–control study of ovarian cancer conducted in New England between 1992 and 2008 with uniform data collected on talc use and douching. We estimated risk for ovarian cancer and other adverse reproductive outcomes associated with douching or genital talc use taking into consideration those factors that may influence why women choose to douche or use talc genitally.

Material and Methods

Data came from the three enrollment phases of the New England–based Case Control Study (phase I 1992–1997; phase II: 1998–2002; and phase III: 2003–2008). Details regarding enrollment are described elsewhere (10). Briefly, 3,957 women residing in Eastern Massachusetts and New Hampshire diagnosed with ovarian cancer between ages 18 and 80 were identified through tumor boards and registries. A total of 874 cases had either died or were ineligible because they had moved outside the study area, did not have a working telephone number, or had a

[1]Department of Obstetrics, Gynecology and Reproductive Biology, Brigham and Women's Hospital, Boston, Massachusetts. [2]Department of Pathology, Brigham and Women's Hospital, Boston, Massachusetts. [3]Department of Epidemiology, University of Dartmouth, Geisel School of Medicine, Hanover, New Hampshire.

Corresponding Author: Daniel W. Cramer, Brigham and Women's Hospital and Harvard Medical School, 221 Longwood Avenue, Boston, MA 02115. Phone: 617-732-4895; Fax: 617-732-4899; E-mail: dcramer@bwh.harvard.edu

Cancer Epidemiol Biomarkers Prev 2019;28:1835–44

doi: 10.1158/1055-9965.EPI-19-0375 Nov (11)

non-ovarian primary tumor. Of the remaining 3,083 cases, 2,203 (71%) were enrolled. After excluding 128 non-epithelial and 35 mixed mesodermal tumors, 2,040 cases with epithelial tumors of ovarian, primary peritoneal, and fallopian tube origin, including borderline malignancies [henceforth, epithelial ovarian cancer (EOC)] were available for analysis.

Controls were identified through random digit dialing, driver license lists, and town-resident lists. Between 1992 and 1997, 420 (72%) women identified through random digit dialing and 102 (51%) women identified through lists agreed to participate. From 1998 to 2008, 4,366 potential controls were identified using the lists, of whom 1,426 (33%) were ineligible because they had died, moved, were too ill to participate, did not have a working phone, did not speak English, or had surgical removal of ovaries. Of eligible controls, 1,362 (46%) declined to participate by phone or via "opt-out" postcard and 1,578 (54%) were enrolled (2,100 total). Controls were frequency matched to cases by 5-year age groups and region of residence.

Exposure and outcome assessment

Subjects were interviewed in-person about potential EOC risk factors that occurred more than 1 year before diagnosis for cases and 1 year before date of interview for controls. Subjects were asked whether they "regularly" or "at least monthly" applied powder to: the genital or rectal area, sanitary napkins or tampons, underwear, or areas other than the genital–rectal area. Additional details included type of powder, age begun, years used, and applications per month. Lifetime exposure was estimated by multiplying the frequency of applications per month by months used. This was divided by 360 (i.e., daily use coded as 30/month) to yield talc-years. To create categorical variables for talc-years, we chose cut-off points based on quartiles for exposed controls and rounded to the nearest integer. Participants were asked whether they ever douched "regularly" and if they did, they were asked to provide the brand name or type of douches used, the age they began using them, and the total years used. We classified type of douche into any use of store-bought douche or homemade douches only. Women who used both store-bought and homemade douches (14 cases and seven controls) and women who said they used deodorant vaginal suppositories (two cases and two controls) were counted with those who used store-bought douches. In addition, we classified age at first use into three categories, <20, 20–29, and ≥30, and years of use into quartiles based on the control distribution of use.

Subjects were also asked about the occurrence of PID, ectopic pregnancy, and cervical neoplasia, the latter based upon either a history of cervical cancer, intraepithelial neoplasia, or abnormal pap smear that required hysterectomy, conization, or a loop electrosurgical excision procedure. PID was assessed only in the last phase of the study, and cervical procedures were recorded only for study phases II–III. Risks for PID, ectopic pregnancy, and cervical neoplasia associated with talc use or douching were examined individually in EOC cases and controls separately.

Pathology reports were collected for all cases and reviewed by a gynecologic pathologist (W.R. Welch). Tumors were classified by behavior and histology (serous borderline, serous invasive, mucinous, endometrioid, clear cell, and other). Undifferentiated and transitional cell carcinomas, fallopian tube primaries, and primary peritoneal tumors were counted as serous. Mixed epithelial, malignant Brenner, and unspecified epithelial tumors were classified as other.

Statistical analysis

χ^2 tests were used to compare characteristics of cases and controls who did or did not douche or use talc in the genital area. We used unconditional logistic regression to estimate ORs and 95% confidence intervals (CI) for EOC. We examined the association between douching and EOC, stratified by genital talc use and the association between talc use and EOC, stratified by douching. We also examined these associations within histologic types of EOC. In addition, we modeled risk of adverse reproductive outcomes (PID, ectopic pregnancy, and cervical neoplasia) separately among cases and controls. Models were adjusted for the study matching factors (age, study center, and phase) and potential confounders including parity (continuous), oral contraceptive use (never, <23 months, 23–49 months, 50–96 months, and >96 months), BMI (continuous), race (white and non-white), diaphragm use (never and ever), spermicide use (never and ever), menopausal status (pre and post), marital status (never and ever married), smoking (never, former, and current), days of menstrual flow (≤5 and >5) and age at menarche (continuous), and tubal sterilization (yes and no). Tests for trend for duration of douching and talc-years were based on the Wald statistic using continuous variables weighted by category midpoints with zero assigned as the exposure for nonusers. Likelihood ratio tests comparing models with and without interaction terms were used to test for effect modification. Because exposure data were censored by date of diagnosis of ovarian cancer and not on the date of the adverse events, dose-response and trend analyses were not performed for those outcomes. Records with missing data for the exposure of interest were excluded from logistic regression models. Among model covariates, data were missing for BMI ($n = 11$), age at menarche ($n = 16$), and race ($n = 2$). Missing data points were assigned to the most common or median value for each variable to allow records with missing data to be included in multivariable models. Analyses were performed using SAS v9.4 (SAS Institute).

Ethical approval

Institutional review boards approved the study. All participants provided written informed consent.

Results

Several factors associated with the likelihood of douching were also associated with likelihood of using talc genitally and were seen in both cases and controls. Women more likely to engage in both practices were: older, postmenopausal, heavier, and married (Table 1). Women who douched were more likely to be smokers, parous, and have had a tubal ligation and less likely to have used oral contraceptives. Cases who used a diaphragm or had a tubal ligation and controls who used spermicides were more likely to have used talc. Among cases, douching and talc use varied by age at menarche but without any apparent trend for the practices to be associated with an earlier or later menarche. Among controls, those who reported more than 5 days of flow were more likely to douche than women with fewer days of flow. Accordingly, in subsequent tables, we adjusted for these factors in looking at risk for EOC or adverse reproductive outcomes.

Overall risk of EOC was not elevated for women who douched, compared with those who did not, OR (95% CI) = 0.98 (0.83–1.17; Table 2). The ORs for douching in relation to EOC were similar among women who used genital talc, OR = 1.03 (95% CI,

www.aacrjournals.org

Published OnlineFirst August 27, 2019; DOI: 10.1158/1055-9965.EPI-19-0375

Table 1. Characteristics of cases and controls by douching and genital talc use

	Douching						Genital talc use					
	Cases			Controls			Cases			Controls		
	No	Yes	*P*	No	Yes	*P*	No	Yes	*P*	No	Yes	*P*
Age, years												
<50	699 (86.3%)	111 (13.7%)	0.001	744 (89.1%)	91 (10.9%)	<0.0001	599 (74.0%)	211 (26.0%)	<0.0001	670 (80.2%)	165 (19.8%)	<0.0001
50–64	683 (80.4%)	166 (19.6%)		705 (80.4%)	172 (19.6%)		541 (63.7%)	308 (36.3%)		599 (68.3%)	278 (31.7%)	
≥65	301 (79.0%)	80 (21.0%)		289 (74.5%)	99 (25.5%)		258 (67.7%)	123 (32.3%)		282 (72.7%)	106 (27.3%)	
Menopausal status												
Pre	776 (86.3%)	123 (13.7%)	<0.0001	830 (89.1%)	102 (10.9%)	<0.0001	652 (72.5%)	247 (27.5%)	0.0006	735 (78.9%)	197 (21.1%)	<0.0001
Post	907 (79.5%)	234 (20.5%)		908 (77.7%)	260 (22.3%)		746 (65.4%)	395 (34.6%)		816 (69.9%)	352 (30.1%)	
Center												
MA	1,343 (83.2%)	272 (16.8%)	0.13	1,424 (83.3%)	285 (16.7%)	0.15	1,082 (67.0%)	533 (33.0%)	0.004	1,232 (72.1%)	477 (27.9%)	0.0001
NH	340 (80.0%)	85 (20.0%)		314 (80.3%)	77 (19.7%)		316 (74.4%)	109 (25.6%)		319 (81.6%)	72 (18.4%)	
Study												
Phase I	460 (82.6%)	97 (17.4%)	0.97	419 (80.3%)	103 (19.7%)	0.13	408 (73.2%)	149 (26.8%)	0.01	430 (82.4%)	92 (17.6%)	<0.0001
Phase II	541 (82.2%)	117 (17.8%)		595 (82.5%)	126 (17.5%)		448 (68.1%)	210 (31.9%)		519 (72.0%)	202 (28.0%)	
Phase III	682 (82.7%)	143 (17.3%)		724 (84.5%)	133 (15.5%)		542 (65.7%)	283 (34.3%)		602 (70.2%)	255 (29.8%)	
Race												
White	1,627 (83.1%)	332 (16.9%)	0.005	1,710 (82.9%)	352 (17.1%)	0.13	1,343 (68.6%)	616 (31.4%)	0.97	1,526 (74.0%)	536 (26.0%)	0.25
Non-white[a]	56 (70.9%)	23 (29.1%)		28 (73.7%)	10 (26.3%)		54 (68.4%)	25 (31.6%)		25 (65.8%)	13 (34.2%)	
BMI[c]												
<20	141 (87.6%)	20 (12.4%)	<0.0001	123 (86.0%)	20 (14.0%)	0.0006	124 (77.0%)	37 (23.0%)	0.004	124 (86.7%)	19 (13.3%)	0.0005
20–24.9	745 (86.3%)	118 (13.7%)		794 (85.3%)	137 (14.7%)		608 (70.5%)	255 (29.5%)		692 (74.3%)	239 (25.7%)	
25–29.9	436 (78.4%)	120 (21.6%)		517 (82.3%)	111 (17.7%)		375 (67.4%)	181 (32.6%)		460 (73.2%)	168 (26.8%)	
≥30	359 (78.4%)	99 (21.6%)		296 (76.1%)	93 (23.9%)		289 (63.1%)	169 (36.9%)		267 (68.6%)	122 (31.4%)	
Smoking status												
Never	825 (86.0%)	134 (14.0%)	<0.0001	876 (87.0%)	131 (13.0%)	<0.0001	668 (69.7%)	291 (30.3%)	0.18	759 (75.4%)	248 (24.6%)	0.23
Former	598 (82.3%)	129 (17.7%)		635 (79.6%)	163 (20.4%)		480 (66.0%)	247 (34.0%)		573 (71.8%)	225 (28.2%)	
Current	260 (73.4%)	94 (26.6%)		227 (76.9%)	68 (23.1%)		250 (70.6%)	104 (29.4%)		219 (74.2%)	76 (25.8%)	
Married												
Never	303 (88.9%)	38 (11.1%)	0.0007	175 (90.7%)	18 (9.3%)	0.002	251 (73.6%)	90 (26.4%)	0.03	153 (79.3%)	40 (20.7%)	0.07
Ever	1,380 (81.2%)	319 (18.8%)		1,563 (82.0%)	344 (18.0%)		1,147 (67.5%)	552 (32.5%)		1,398 (73.3%)	509 (26.7%)	
Parity												
Nulliparous	572 (88.1%)	77 (11.9%)	<0.0001	335 (88.6%)	43 (11.4%)	0.0009	454 (70.0%)	195 (30.0%)	0.34	284 (75.1%)	94 (24.9%)	0.53
Parous	1,111 (79.9%)	280 (20.1%)		1,403 (81.5%)	319 (18.5%)		944 (67.9%)	447 (32.1%)		1,267 (73.6%)	455 (26.4%)	
OC use												
Never	786 (80.7%)	188 (19.3%)	0.04	612 (79.9%)	154 (20.1%)	0.008	672 (69.0%)	302 (31.0%)	0.67	559 (73.0%)	207 (27.0%)	0.49
Ever	897 (84.1%)	169 (15.9%)		1,126 (84.4%)	208 (15.6%)		726 (68.1%)	340 (31.9%)		992 (74.4%)	342 (25.6%)	
Tubal ligation												
No	1,471 (83.4%)	292 (16.6%)	0.005	1,406 (83.6%)	275 (16.4%)	0.03	1,222 (69.3%)	541 (30.7%)	0.05	1,241 (73.8%)	440 (26.2%)	0.95
Yes	212 (76.5%)	65 (23.5%)		332 (79.2%)	87 (20.8%)		176 (63.5%)	101 (36.5%)		310 (74.0%)	109 (26.0%)	
Diaphragm												
No	1,208 (82.1%)	264 (17.9%)	0.41	1,190 (82.1%)	259 (17.9%)	0.25	1,031 (70.0%)	441 (30.0%)	0.02	1,079 (74.5%)	370 (25.5%)	0.34
Yes	475 (83.6%)	93 (16.4%)		548 (84.2%)	103 (15.8%)		367 (64.6%)	201 (35.4%)		472 (72.5%)	179 (27.5%)	
Spermicides												
No	1,549 (82.8%)	322 (17.2%)	0.25	1,586 (82.7%)	332 (17.3%)	0.78	1,286 (68.7%)	585 (31.3%)	0.51	1,432 (74.7%)	486 (25.3%)	0.007
Yes	134 (79.3%)	35 (20.7%)		152 (83.5%)	30 (16.5%)		112 (66.3%)	57 (33.7%)		119 (65.4%)	63 (34.6%)	
Amount of flow												
Light/moderate	994 (82.9%)	205 (17.1%)	0.45	1,019 (83.7%)	199 (16.3%)	0.13	838 (69.9%)	361 (30.1%)	0.09	898 (73.7%)	320 (26.3%)	0.98
Moderate heavy/heavy	674 (81.6%)	152 (18.4%)		690 (81.1%)	161 (18.9%)		548 (66.3%)	278 (33.7%)		627 (73.7%)	224 (26.3%)	

(Continued on the following page)

Published OnlineFirst August 27, 2019; DOI: 10.1158/1055-9965.EPI-19-0372

Table 1. Characteristics of cases and controls by douching and genital talc use (Cont'd.)

	Douching						Genital talc use					
	Cases			Controls			Cases			Controls		
	No	Yes	*P*	No	Yes	*P*	No	Yes	*P*	No	Yes	*P*
Age at menarche, years												
<12	347 (80.7%)	83 (19.3%)	0.01	344 (81.3%)	79 (18.7%)	0.65	286 (66.5%)	144 (33.5%)	0.02	311 (73.5%)	112 (26.5%)	0.93
12–13	976 (83.3%)	195 (16.7%)		980 (83.5%)	194 (16.5%)		786 (67.1%)	385 (32.9%)		872 (74.3%)	302 (25.7%)	
14	198 (86.8%)	30 (13.2%)		202 (83.5%)	40 (16.5%)		175 (76.8%)	53 (23.2%)		175 (72.3%)	67 (27.7%)	
>14	154 (75.9%)	49 (24.1%)		205 (81.0%)	48 (19.0%)		145 (71.4%)	58 (28.6%)		186 (73.5%)	67 (26.5%)	
Days of flow												
≤5	1,128 (82.5%)	239 (17.5%)	0.92	1,192 (83.8%)	230 (16.2%)	0.05	935 (68.4%)	432 (31.6%)	0.96	1,033 (72.6%)	389 (27.4%)	0.07
>5	541 (82.3%)	116 (17.7%)		534 (80.3%)	131 (19.7%)		450 (68.5%)	207 (31.5%)		508 (76.4%)	157 (23.6%)	

Abbreviation: OC, oral contraceptive.
[a]Non-white race includes 58 African American, 64 Hispanic, 46 Asian, and 9 Other race women.
[b]BMI is missing for two cases and nine controls.

0.77–1.38) and those who did not, OR = 0.94 (95% CI, 0.76–1.16). Excluding women with tubal ligation (rather than adjusting for it) did not materially change these estimates; OR = 0.98 (95% CI, 0.81–1.19) for douching overall, OR = 1.09 (95% CI, 0.79–1.52) for douching and talc, and OR = 0.93 (95% CI, 0.73–1.18) for douching alone. No trends in overall risk for EOC were associated with age-at-first use of douching or years of douching overall or in subgroups of women who used or did not use talc. Risk of EOC overall appeared to be decreased with use of "homemade" douching products OR (95% CI), 0.78 (0.60–1.02) whereas risk was increased with use of "store-bought" products, OR = 1.11 (0.91–1.37), but neither association was statistically significant. This difference was more apparent among women who used talc but did not reach significance in tests for heterogeneity (see Table 2 footnote).

In Table 3, we show the findings for talc use overall and in analyses stratified by douching. Women who used talc had an elevated risk for EOC overall compared with those who did not, OR (95% CI), 1.30 (1.13–1.50). The ORs for talc use in relation to EOC were similar among women who had also regularly douched, OR, 1.32 (95% CI, 0.95–1.82) and those who had not, OR, 1.28 (95% CI, 1.09–1.51). Excluding women with tubal ligation slightly lowered these estimates but did not change their significance; OR, 1.23 (95% CI, 1.05–1.44) for talc use overall, OR, 1.33 (95% CI, 0.92–1.92) for talc and douching, and OR, 1.19 (95% CI, 1.00–1.42) for talc alone. Risks were greater for women who began talc use during their 20s, and this was true regardless of whether the woman also douched. Risk of EOC increased significantly with increasing talc-years and the trend was more apparent in women who did not regularly douche. The ORs associated with ever-use of talc, age-at-first use, and talc-years of use were not significantly different among women who had also douched and those who had not (see Table 3 footnote).

Table 4 examines risk for EOC overall and for specific histologic types of ovarian cancer in four mutually exclusive usage categories: women who never douched or used talc, women who used talc but did not douche, women who douched but did not use talc, and women who both douched and used talc. Douching, compared with neither douching nor using talc, did not increase risk for EOC overall or histologic subtypes, and this was true whether the douching product was store-bought or homemade.

Compared with not douching or using talc, the OR for using talc was elevated for EOC overall (OR, 1.29; 95% CI, 1.10–1.51), for serous borderline tumors (OR, 1.39; 95% CI, 0.99–1.97), and for serous invasive tumors (OR, 1.39; 95% CI, 1.14–1.69). The associations were slightly stronger for women who used talc and store-bought douches, compared with those who used neither; OR, 1.53 (95% CI, 1.11–2.10) for EOC overall, OR, 2.11 (95% CI, 1.13–3.96) for serous borderline, and OR, 1.57 (95% CI, 1.07–2.31) for serous invasive tumors. Risk for the endometrioid subtype was elevated for those who used talc and store-bought douches compared with talc use without douching, but the association was not statistically significant. Although these findings are suggestive of an interaction between talc use and store-bought douches, formal tests for interaction did not reach the level of statistical significance (see Table 4 footnote).

Table 5 shows the risk for PID, ectopic pregnancy, and cervical neoplasia in cases and controls separately, again by the mutually exclusive categories related to talc and type of douche used. Relative to cases who neither douched nor used talc, elevated risks for PID were found for cases who used a store-bought douche

Published OnlineFirst August 27, 2019; DOI: 10.1158/1055-9965.EPI-19-0373

Table 2. Associations between douching and ovarian cancer by talc use

Douching	Controls *N* (%)	Cases *N* (%)	Crude OR (95% CI)	Adjusted OR (95% CI)[a]	P^a
All cases and controls					
Douched regularly					
No	1,738 (82.8)	1,683 (82.5)	1.00 (reference)	1.00 (reference)	
Yes	362 (17.2)	357 (17.5)	1.02 (0.87–1.20)	0.98 (0.83–1.17)	0.85
Age at first use, years					
<20	90 (4.3)	100 (4.9)	1.15 (0.86–1.54)	1.12 (0.82–1.52)	0.48
20–29	217 (10.4)	184 (9.0)	0.88 (0.71–1.08)	0.84 (0.68–1.05)	0.12
≥30	51 (2.4)	68 (3.3)	1.38 (0.95–1.99)	1.34 (0.91–1.97)	0.14
Duration of douching					
≤5 years	92 (4.4)	94 (4.6)	1.06 (0.79–1.42)	1.04 (0.76–1.41)	0.82
6–15 years	92 (4.4)	101 (5.0)	1.13 (0.85–1.52)	1.12 (0.83–1.52)	0.46
16–26 years	87 (4.2)	72 (3.5)	0.86 (0.62–1.18)	0.80 (0.57–1.11)	0.18
>26 years	87 (4.2)	84 (4.1)	1.00 (0.73–1.36)	0.93 (0.67–1.29)	0.68
P_{trend}					0.50
Type of douche used					
Store-bought	217 (10.3)	239 (11.7)	1.14 (0.94–1.38)	1.11 (0.91–1.37)	0.30
Homemade	142 (6.8)	114 (5.6)	0.83 (0.64–1.07)	0.78 (0.60–1.02)	0.07
Among talc users					
Douched regularly[b]					
No	428 (78.0)	496 (77.3)	1.00 (reference)	1.00 (reference)	
Yes	121 (22.0)	146 (22.7)	1.04 (0.79–1.37)	1.03 (0.77–1.38)	0.84
Age at first use, years[c]					
<20	26 (4.8)	45 (7.1)	1.49 (0.91–2.46)	1.45 (0.85–2.46)	0.17
20–29	74 (13.5)	71 (11.1)	0.83 (0.58–1.18)	0.82 (0.57–1.19)	0.29
≥30	19 (3.5)	26 (4.1)	1.18 (0.64–2.16)	1.17 (0.62–2.20)	0.64
Duration of douching[d]					
≤5 years	27 (4.9)	33 (5.2)	1.05 (0.62–1.78)	1.12 (0.65–1.93)	0.68
6–15 years	32 (5.9)	43 (6.7)	1.16 (0.72–1.87)	1.18 (0.72–1.95)	0.51
16–26 years	30 (5.5)	29 (4.5)	0.83 (0.49–1.41)	0.69 (0.39–1.21)	0.20
>26 years	29 (5.3)	37 (5.8)	1.10 (0.67–1.82)	1.09 (0.64–1.87)	0.75
P_{trend}					0.91
Type of douche used[e]					
Store-bought	75 (13.7)	108 (16.9)	1.24 (0.90–1.71)	1.22 (0.87–1.71)	0.25
Homemade	45 (8.2)	35 (5.5)	0.67 (0.42–1.06)	0.67 (0.41–1.10)	0.11
Among those who never used talc					
Douched regularly[b]					
No	1,310 (84.5)	1,187 (84.9)	1.00 (reference)	1.00 (reference)	
Yes	241 (15.5)	211 (15.1)	0.97 (0.79–1.18)	0.94 (0.76–1.16)	0.58
Age at first use, years[c]					
<20	64 (4.1)	55 (3.9)	0.95 (0.66–1.37)	0.94 (0.63–1.39)	0.74
20–29	143 (9.2)	113 (8.1)	0.87 (0.67–1.13)	0.84 (0.64–1.10)	0.20
≥30	32 (2.1)	42 (3.0)	1.45 (0.91–2.31)	1.48 (0.91–2.42)	0.11
Duration of douching[d]					
≤5 years	65 (4.2)	61 (4.4)	1.04 (0.72–1.48)	1.00 (0.69–1.44)	0.98
6–15 years	60 (3.9)	58 (4.2)	1.07 (0.74–1.54)	1.08 (0.74–1.59)	0.69
16–26 years	57 (3.7)	43 (3.1)	0.83 (0.56–1.25)	0.83 (0.55–1.27)	0.40
>26 years	58 (3.7)	47 (3.4)	0.89 (0.60–1.32)	0.81 (0.54–1.24)	0.33
P_{trend}					0.33
Type of douche used[e]					
Store-bought	142 (9.2)	131 (9.4)	1.02 (0.79–1.31)	1.01 (0.78–1.32)	0.92
Homemade	97 (6.3)	79 (5.7)	0.90 (0.66–1.22)	0.85 (0.61–1.18)	0.33

NOTE: The following variables have missing data: age at first use ($n = 9$), duration ($n = 10$), and type of douche ($n = 7$).
[a]Adjusted for age, study center and phase, menopausal status, marital status, parity, oral contraceptive use and duration, tubal ligation, BMI, race, diaphragm use, spermicide use, smoking, days of menstrual flow, and age at menarche.
[b]$P_{heterogeneity} = 0.79$.
[c]$P_{heterogeneity} = 0.43$.
[d]$P_{heterogeneity} = 0.91$.
[e]$P_{heterogeneity} = 0.50$.

alone OR, 4.44 (95% CI, 1.22–16.1) and for those who used a store-bought douche and talc, OR, 5.46 (95% CI, 1.64–18.2). An elevated risk for cervical neoplasia in cases who used homemade douches was also seen. Risk estimates for these associations were imprecise as illustrated by their wide CIs. For controls, none of the ORs reached significance nor were differences in risk found by whether homemade or store-bought douches were used.

Discussion

Using data from a case–control study of ovarian cancer, we examined the role of douching as a risk factor for EOC independent of talc use and, conversely, whether talc use affects risks for adverse reproductive outcomes that have been associated with douching such as PID. Examined as separate variables, douching

Published OnlineFirst August 27, 2019; DOI: 10.1158/1055-9965.EPI-19-0378

Table 3. Associations between genital talc use and ovarian cancer by douching

Genital talc use	Controls *N* (%)	Cases *N* (%)	Crude OR (95% CI)	Adjusted OR (95% CI)[a]	*P*[a]
All cases and controls					
Ever used					
No	1,551 (73.9)	1,398 (68.5)	1.00 (reference)	1.00 (reference)	
Yes	549 (26.1)	642 (31.5)	1.30 (1.13–1.48)	1.30 (1.13–1.50)	0.0003
Age at first use, years					
<20	343 (16.4)	363 (17.9)	1.17 (1.00–1.38)	1.15 (0.97–1.37)	0.10
20–29	122 (5.8)	183 (9.0)	1.66 (1.31–2.12)	1.73 (1.35–2.23)	<0.0001
≥30	76 (3.6)	87 (4.3)	1.27 (0.93–1.74)	1.25 (0.90–1.74)	0.18
Talc-years					
≤1 talc-year	138 (6.6)	138 (6.8)	1.11 (0.87–1.42)	1.12 (0.86–1.45)	0.40
>1–5 talc-years	124 (5.9)	148 (7.3)	1.32 (1.03–1.70)	1.37 (1.05–1.77)	0.02
>5–24 talc-years	146 (7.0)	170 (8.4)	1.29 (1.02–1.63)	1.24 (0.97–1.58)	0.08
>26 talc-years	127 (6.1)	171 (8.4)	1.49 (1.17–1.90)	1.51 (1.17–1.95)	0.001
P_{trend}					0.0001
Among women who douched					
Ever used[b]					
No	241 (66.6)	211 (59.1)	1.00 (reference)	1.00 (reference)	
Yes	121 (33.4)	146 (40.9)	1.38 (1.02–1.87)	1.32 (0.95–1.82)	0.10
Age at first use, years[c]					
<20	80 (22.2)	85 (23.9)	1.21 (0.85–1.73)	1.15 (0.78–1.69)	0.47
20–29	25 (6.9)	45 (12.6)	2.06 (1.22–3.47)	2.04 (1.17–3.55)	0.01
≥30	14 (3.9)	15 (4.2)	1.22 (0.58–2.59)	1.19 (0.54–2.62)	0.67
Talc-years[d]					
≤1 talc-year	24 (6.7)	26 (7.3)	1.24 (0.69–2.22)	1.31 (0.69–2.47)	0.41
>1–5 talc-years	19 (5.3)	30 (8.5)	1.80 (0.99–3.30)	1.89 (1.00–3.57)	0.05
>5–24 talc-years	40 (11.1)	40 (11.3)	1.14 (0.71–1.84)	0.95 (0.57–1.59)	0.85
>26 talc-years	36 (10.0)	47 (13.3)	1.49 (0.93–2.39)	1.47 (0.90–2.43)	0.13
P_{trend}					0.15
Among women who did not douche					
Ever used[b]					
No	1,310 (75.4)	1,187 (70.5)	1.00 (reference)	1.00 (reference)	
Yes	428 (24.6)	496 (29.5)	1.28 (1.10–1.49)	1.28 (1.09–1.51)	0.002
Age at first use, years[c]					
<20	263 (15.2)	278 (16.6)	1.17 (0.97–1.41)	1.15 (0.94–1.39)	0.17
20–29	97 (5.6)	138 (8.2)	1.57 (1.20–2.06)	1.63 (1.23–2.16)	0.0007
≥30	62 (3.6)	72 (4.3)	1.28 (0.90–1.82)	1.27 (0.88–1.84)	0.19
Talc-years[d]					
≤1 talc-year	114 (6.6)	112 (6.7)	1.08 (0.83–1.42)	1.08 (0.82–1.44)	0.58
>1–5 talc-years	105 (6.1)	118 (7.1)	1.24 (0.94–1.63)	1.30 (0.98–1.73)	0.07
>5–24 talc-years	106 (6.1)	130 (7.8)	1.35 (1.04–1.77)	1.31 (0.99–1.73)	0.06
>26 talc-years	91 (5.3)	124 (7.4)	1.50 (1.13–1.99)	1.51 (1.12–2.03)	0.007
P_{trend}					0.0006

NOTE: The following variables have missing data: age at first use ($n = 17$) and talc-years ($n = 29$).

[a]Adjusted for age, study center and phase, menopausal status, marital status, parity, oral contraceptive use and duration, tubal ligation, BMI, race, diaphragm use, spermicide use, smoking, days of menstrual flow, and age at menarche.

[b]$P_{heterogeneity} = 0.79$.

[c]$P_{heterogeneity} = 0.85$.

[d]$P_{heterogeneity} = 0.76$.

was not an independent risk factor for ovarian cancer while genital talc use, with or without douching, increased the risk for ovarian cancer. Compared with women who neither douched nor used talc, elevated risks, especially for serous borderline and serous invasive cancer, were seen for women who used talc but did not douche, as well as for women who used talc and, also, douched with a store-bought product. In our analysis, we adjusted for menopausal and marital status, BMI, race, menstrual factors, and contraceptives used including tubal ligation.

The first study to address risk for ovarian cancer associated with douching was also one of the first epidemiologic studies of ovarian cancer (12). McGowan and colleagues found that women with ovarian cancer did not differ from controls in their regular use of douches, consistency of use, age began, or years of use. An early study on talc and ovarian cancer examined douching as a potential confounding factor and found adjustment for it did not negate the talc association (13). Subsequent studies on talc and ovarian cancer did not look at douching either as a confounder or an independent risk factor for ovarian cancer, and the issue was not readdressed until the Gonzalez and colleagues' Sister Study in 2017 (11). The "Sister Study" followed sisters of women who had been diagnosed with breast cancer for new occurrence of ovarian cancer. This study reported that douching (in the previous 12 months) was associated with an OR (95% CI) risk for ovarian cancer of 1.84 (1.2–2.8) while talc use (in the previous 12 months) was not, 0.73 (0.44–1.2).

Related both to the positive finding with douching and null association with talc in the Gonzalez and colleagues study, several issues should be considered. Because more than one sister from a family could have been enrolled, the authors used a statistical technique to adjust for number of family units. It is not clear whether this technique used the actual number of family units

www.aacrjournals.org

Published OnlineFirst August 27, 2019; DOI: 10.1158/1055-9965.EPI-19-0375

Table 4. Associations between douching and genital talc use and ovarian cancer by histologic type

			No talc use, douched			Talc use and douched		
	Never used talc or douched	Talc use, no douching	Any type of douche	Store-bought douche	Homemade douche	Any type of douche	Store-bought douche[a]	Homemade douche[b]
Controls								
N (%)	1,310 (62.5)	428 (20.4)	239 (11.4)	142 (6.8)	97 (4.6)	120 (5.8)	75 (3.6)	45 (2.2)
All cases								
N (%)	1,187 (58.3)	496 (24.4)	210 (10.3)	131 (6.4)	79 (3.9)	143 (7.0)	108 (5.3)	35 (1.7)
OR (95% CI)[c]	1.00 (reference)	1.29 (1.10–1.51)	0.95 (0.77–1.18)	1.02 (0.79–1.33)	0.85 (0.62–1.17)	1.27 (0.97–1.17)	1.53 (1.11–2.10)	0.83 (0.52–1.33)
P[c]		0.002	0.65	0.87	0.32	0.32	0.009	0.44
Serous borderline cases								
N (%)	149 (60.1)	57 (23.0)	26 (10.5)	18 (7.3)	8 (3.2)	16 (6.5)	15 (6.0)	1 (0.4)
OR (95% CI)[c]	1.00 (reference)	1.39 (0.99–1.97)	1.26 (0.79–2.02)	1.28 (0.74–2.22)	1.22 (0.56–2.65)	1.52 (0.84–2.75)	2.11 (1.13–3.96)	0.28 (0.04–2.18)
P[c]		0.06	0.33	0.38	0.62	0.17	0.02	0.23
Serous invasive cases								
N (%)	521 (54.0)	256 (26.5)	109 (11.3)	66 (6.8)	43 (4.5)	79 (8.2)	53 (5.5)	26 (2.7)
OR (95% CI)[c]	1.00 (reference)	1.39 (1.14–1.69)	0.96 (0.74–1.24)	1.11 (0.81–1.54)	0.77 (0.52–1.14)	1.40 (1.02–1.92)	1.57 (1.07–2.31)	1.12 (0.67–1.88)
P[c]		0.001	0.75	0.51	0.19	0.04	0.02	0.67
Mucinous								
N (%)	167 (69.0)	45 (18.6)	21 (8.7)	15 (6.2)	6 (2.5)	9 (3.7)	6 (2.5)	3 (1.2)
OR (95% CI)[c]	1.00 (reference)	0.97 (0.68–1.40)	0.84 (0.51–1.39)	0.91 (0.50–1.63)	0.72 (0.30–1.72)	0.64 (0.31–1.35)	0.62 (0.25–1.54)	0.68 (0.20–2.31)
P[c]		0.89	0.50	0.74	0.46	0.24	0.30	0.54
Endometrioid								
N (%)	201 (60.7)	85 (25.7)	22 (6.6)	15 (4.5)	7 (2.1)	23 (6.9)	18 (5.4)	5 (1.5)
OR (95% CI)[c]	1.00 (reference)	1.26 (0.94–1.69)	0.67 (0.41–1.10)	0.71 (0.40–1.26)	0.61 (0.27–1.38)	1.40 (0.85–2.32)	1.74 (0.98–3.09)	0.82 (0.31–2.18)
P[c]		0.13	0.11	0.24	0.24	0.19	0.06	0.69
Clear cell								
N (%)	74 (63.8)	25 (21.6)	11 (9.5)	7 (6.0)	4 (3.4)	6 (5.2)	6 (5.2)	0 (0)
OR (95% CI)[c]	1.00 (reference)	1.08 (0.66–1.78)	0.99 (0.50–1.95)	1.04 (0.46–2.39)	0.88 (0.30–2.60)	0.96 (0.39–2.36)	1.47 (0.58–3.70)	—
P[c]		0.76	0.97	0.92	0.82	0.93	0.41	—

[a]*P* value comparing talc use (no douching) versus talc use (and douching with store-bought product): all, $P = 0.32$; serous borderline, $P = 0.21$; serous invasive, $P = 0.54$; mucinous, $P = 0.35$; endometrioid, $P = 0.29$; and clear cell, $P = 0.54$.

[b]*P* value comparing talc use (no douching) versus talc use (and douching with homemade product): all, $P = 0.07$; serous borderline, $P = 0.13$; serous invasive, $P = 0.4$; mucinous, $P = 0.58$; and endometrioid, $P = 0.40$.

[c]Adjusted for age, study center and phase, menopausal status, marital status, parity, oral contraceptive use and duration, tubal ligation, BMI, race, diaphragm use, spermicide use, smoking, days of menstrual flow, and age at menarche.

Published OnlineFirst August 27, 2019; DOI: 10.1158/1055-9965.EPI-19-0375

Table 5. Adverse reproductive outcomes among ovarian cancer cases and controls

	Cases					Controls				
	No *N* (%)	Yes *N* (%)	Crude OR (95% CI)	Adjusted OR (95% CI)[a]	*P*[a]	No *N* (%)	Yes *N* (%)	Crude OR (95% CI)	Adjusted OR (95% CI)[a]	*P*[a]
Outcome: PID[b]										
Never used talc or douched	450 (56.5)	11 (39.3)	1.00 (reference)	1.00 (reference)		511 (61.2)	12 (63.2)	1.00 (reference)	1.00 (reference)	
Talc use, no douching	214 (26.9)	7 (25.0)	1.34 (0.51–3.50)	1.41 (0.52–3.83)	0.50	192 (23.0)	7 (36.8)	1.55 (0.60–4.00)	1.70 (0.62–4.66)	0.30
Douched (store-bought), no talc use	50 (6.3)	4 (14.3)	3.27 (1.00–10.7)	4.44 (1.22–16.1)	0.02	49 (5.9)	0 (0)	—	—	—
Douched (homemade), no talc use	27 (3.4)	0 (0)	—	—	—	27 (3.2)	0 (0)	—	—	—
Both talc and douche (store-bought) use	41 (5.1)	5 (17.9)	4.99 (1.65–15.0)	5.46 (1.64–18.2)	0.006	37 (4.4)	0 (0)	—	—	—
Both talc and douche (homemade) use	15 (1.9)	1 (3.6)	2.73 (0.33–22.5)	3.62 (0.36–36.0)	0.27	19 (2.3)	0 (0)	—	—	—
Outcome: ectopic pregnancy[c]										
Never used talc or douched	841 (55.9)	14 (56.0)	1.00 (reference)	1.00 (reference)		1,091 (61.3)	26 (66.7)	1.00 (reference)	1.00 (reference)	
Talc use, no douching	367 (24.4)	6 (24.0)	0.99 (0.38–2.58)	1.14 (0.42–3.10)	0.80	363 (20.4)	7 (17.9)	0.81 (0.35–1.89)	0.90 (0.38–2.13)	0.80
Douched (store-bought), no talc use	105 (7.0)	3 (12.0)	1.72 (0.49–6.09)	2.02 (0.51–7.96)	0.32	130 (7.3)	2 (5.1)	0.65 (0.15–2.76)	0.68 (0.16–2.98)	0.61
Douched (homemade), no talc use	74 (4.9)	0 (0)	—	—	—	92 (5.2)	1 (2.6)	0.46 (0.06–3.41)	0.52 (0.07–4.07)	0.53
Both talc and douche (store-bought) use	87 (5.8)	2 (8.0)	1.39 (0.31–6.20)	2.08 (0.43–10.1)	0.36	64 (3.6)	3 (7.7)	1.97 (0.58–6.69)	2.42 (0.67–8.70)	0.18
Both talc and douche (homemade) use	30 (2.0)	0 (0)	—	—	—	41 (2.3)	0 (0)	—	—	—
Outcome: cervical neoplasia[d]										
Never used talc or douched	797 (57.0)	45 (53.6)	1.00 (reference)	1.00 (reference)		904 (61.1)	53 (54.6)	1.00 (reference)	1.00 (reference)	
Talc use, no douching	361 (25.8)	20 (23.8)	0.98 (0.57–1.69)	1.05 (0.60–1.82)	0.88	333 (22.5)	29 (29.9)	1.49 (0.93–2.38)	1.50 (0.92–2.46)	0.10
Douched (store-bought), no talc use	92 (6.6)	4 (4.8)	0.77 (0.27–2.19)	0.83 (0.28–2.42)	0.73	103 (7.0)	5 (5.2)	0.83 (0.32–2.12)	0.88 (0.33–2.32)	0.80
Douched (homemade), no talc use	47 (3.4)	5 (6.0)	1.88 (0.71–4.97)	3.28 (1.17–9.22)	0.02	51 (3.4)	4 (4.1)	1.34 (0.47–3.85)	1.58 (0.53–4.77)	0.41
Both talc and douche (store-bought) use	77 (5.5)	8 (9.5)	1.84 (0.84–4.04)	1.94 (0.85–4.43)	0.12	57 (3.9)	5 (5.2)	1.50 (0.58–3.89)	1.40 (0.51–3.82)	0.52
Both talc and douche (homemade) use	25 (1.8)	2 (2.4)	1.42 (0.33–6.17)	1.88 (0.41–8.64)	0.41	32 (2.2)	1 (1.0)	0.53 (0.07–3.98)	0.45 (0.06–3.49)	0.44

[a]Adjusted for age, study center and phase, parity, oral contraceptive use and duration, tubal ligation, BMI, race, diaphragm use, spermicide use, menopausal status, and smoking.
[b]Study phase III only.
[c]Among those ever pregnant.
[d]Study phases II–III only.

which, ideally, should have been explicitly shown in their Table 1. This is important, because 69% of women in a survey related to douching said they learned the habit from a mother or sister (3). Any genital exposure to talc in the prior year was defined by aggregating several types of exposure including use on sanitary napkins or barrier contraceptive devices. This is problematic because these types of talc exposures would not pertain to the 69% of postmenopausal cases in the study. Also, not counted would be those who had recently discontinued talc use (perhaps because of recent publicity regarding talc use and ovarian cancer association). In fact, only 14% of the cohort reported genital talc exposure in this study, far lower than the other two cohort studies, 40.4% in the Nurses' Health Study (14) and 52.6% in the Women's Health Initiative (15). Finally, an OR of 0.73 for ovarian cancer with talc reported from the Sister Study stands out as the clearest outlier in a recent meta-analysis of studies on talc and ovarian cancer (16).

Among the 362 (17.2%) controls in our study who reported regular douching, 106 (28.5%) said they used homemade vinegar and water and 25 (6.7%) used tap water, leaving about 65% who used store-bought products, with Massengill and Summer's Eve most commonly reported. However, within specific brands, multiple products are offered (e.g., medicated douches, cleansing douches, vinegar and water, and douches with different fragrances, etc.). This level of detail was not obtained in our study so the only distinction we could make was store-bought versus homemade. Notably the combination of talc-use and douching with a homemade product was associated with a reduced risk for ovarian cancer, while douching with a store-bought product with a nonsignificantly elevated risk (Table 2). In addition, compared with women who neither douched nor used talc and women who both used talc and store-bought douches had modestly higher risks for ovarian cancer overall and borderline and invasive serous cancer compared with those who used talc but did not douche. However, this apparent interaction did not reach statistical significance. No interaction between douching and talc use was seen in the Sister Study but they did not report information on type of douching product used, even at the level of store-bought or homemade.

Chemicals used in commercial douching products include emulsifiers and surfactant cleansers like octoxynol-9 and preservatives like sodium benzoate, methylchloroisothiazolinone, and citric acid, and "fragrances" which could include any of thousands of amines, aromatics, esters, and terpenes. It is likely that most of these chemicals would be capable of absorption through the vaginal mucosa. This is certainly true for the preservatives used in douches, which are capable of causing sensitization and allergic reactions (17). Pointing to a study which found women who douched had higher levels of urinary metabolites of phthalates (18), Gonzalez and colleagues suggested this may be the agent that explains why douching may increase the risk for ovarian cancer. Presence of phthalates in douches was assumed because phthalates may be used as carrier molecule for fragrances (18); but douches have not been specifically examined in studies that measured phthalates in a wide variety of personal care products (19–22). While our data cannot point to specific agents that might account for possible differences in risk for ovarian cancer between store-bought and homemade douches, the fact that differences between the two have been described for risk of other adverse reproductive health events (4, 5, 9) suggests this is likely to be a meaningful dichotomy.

In this study, we also had the opportunity to look at whether talc use can increase the risk for events that have been associated with douching including PID, ectopic pregnancy, or cervical neoplasia. In controls, neither douching nor talc use nor their combination was found to affect risks for these adverse outcomes. However, cases who douched with a store-bought product had an elevated risk for PID, regardless of whether they used talc. Furthermore, risk for cervical neoplasia was increased by use of homemade douches. Chance must be considered as an explanation for all these associations. A major limitation associated with this aim of our study is the fact that adverse events, other than ovarian cancer, were not the specific focus of our study, but collected as part of the participants' health histories. Thus, our study was not powered to detect the associations examined here with any set level of confidence. In addition, for the non-ovarian cancer adverse events, only the ever-never association could be examined. Dose-related information on douching or talc use could not be used because these had been censored on the date of the ovarian cancer diagnosis or interview and not on the date when the other adverse event occurred. This issue also affects how to deal with closure of the female tract by tubal ligation (or hysterectomy) where some might advocate truncating the exposure for age as closure as we did for talc (10). However, exclusion of women with tubal ligation did not alter key results from Tables 2 and 3. Finally, a more general concern in case–control studies is the issue of recall bias. We previously addressed this issue in our 2016 article and pointed out several arguments against recall bias as an explanation including: no association with non-genital talc use or starch-based products, variation in risk by histologic type of ovarian cancer, and stronger association with regular use than ever-use (10).

In conclusion, our study found that douching is not an independent risk factor for ovarian cancer nor did it raise the risk for EOC beyond that for talc use alone. However, there was suggestive evidence that the combination of talc and store-bought douches may add to the risks from talc use alone. A distinction between store-bought and homemade douches suggests a possible role for chemicals used in commercial douching products. Reexamination of existing studies that have information on both variables would be helpful in verifying the associations described here. Important and relevant information may also come from *in vitro* and *in vivo* studies, which look at the combined effects of talc and the chemicals found in douching products as they may affect ovarian or tubal inflammation.

Disclosure of Potential Conflicts of Interest

A.F. Vitonis has provided statistical programming to support expert testimony for Beasley Allen Law Firm. D.W. Cramer has provided expert testimony for Beasley Allen Law Firm. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: I.M. Gabriel, L. Titus, D.W. Cramer
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): W.R. Welch, L. Titus, D.W. Cramer
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): A.F. Vitonis, D.W. Cramer
Writing, review, and/or revision of the manuscript: I.M. Gabriel, A.F. Vitonis, L. Titus, D.W. Cramer
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): A.F. Vitonis, L. Titus
Study supervision: L. Titus

Acknowledgments

This work was supported by the NIH grant nos. R01CA054419 and P50CA105009 (to D.W. Cramer), R01HD071021 and HHSN261201500027C (to L. Titus), and the Department of Obstetrics and Gynecology, Brigham and Women's Hospital.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received April 4, 2019; revised July 1, 2019; accepted August 16, 2019; published first August 27, 2019.

References

1. Aral SO, Mosher WD, Cates W Jr. Vaginal douching among women of reproductive age in the United States: 1988. Am J Public Health 1992;82:210–4.
2. Rosenblatt KA, Mathews WA, Daling JR, Voigt LF, Malone K. Characteristics of women who use perineal powders. Obstet Gynecol 1998;92:753–6.
3. Brown JM, Poirot E, Hess KL, Brown S, Vertucci M, Hezareh M. Motivations for intravaginal product use among a cohort of women in Los Angeles. PLoS One 2016;11:e0151378.
4. Scholes D, Daling JR, Stergachis A, Weiss NS, Wang SP, Grayston JT. Vaginal douching as a risk factor for acute pelvic inflammatory disease. Obstet Gynecol 1993;81:601–6.
5. Chow WH, Daling JR, Weiss NS, Moore DE, Soderstrom R. Vaginal douching as a potential risk factor for tubal ectopic pregnancy. Am J Obstet Gynecol 1985;153:727–9.
6. Peters RK, Thomas D, Hagan DG, Mack TM, Henderson BE. Risk factors for invasive cervical cancer among Latinas and non-Latinas in Los Angeles County. J Natl Cancer Inst 1986;77:1063–77.
7. Zhang J, Thomas AG, Leybovich E. Vaginal douching and adverse health effects: a meta-analysis. Am J Public Health 1997;87:1207–11.
8. Klebanoff MA, Nansel TR, Brotman RM, Zhang J, Yu KF, Schwebke JR, et al. Personal hygienic behaviors and bacterial vaginosis. Sex Transm Dis 2010;37:94–9.
9. Spinillo A, Pizzoli G, Colonna L, Nicola S, De Seta F, Guaschino S. Epidemiologic characteristics of women with idiopathic recurrent vulvovaginal candidiasis. Obstet Gynecol 1993;81:721–7.
10. Cramer DW, Vitonis AF, Terry KL, Welch WR, Titus LJ. The association between talc use and ovarian cancer: a retrospective case-control study in two US states. Epidemiology 2016;27:334–46.
11. Gonzalez NL, O'Brien KM, D'Aloisio AA, Sandler DP, Weinberg CR. Douching, talc use, and risk of ovarian cancer. Epidemiology 2016;27:797–802.
12. McGowan L, Parent L, Lednar W, Norris HJ. The woman at risk for developing ovarian cancer. Gynecol Oncol 1979;7:325–44.
13. Harlow BL, Cramer DW, Bell DA, Welch WR. Perineal exposure to talc and ovarian cancer risk. Obstet Gynecol 1992;80:19–26.
14. Gertig DM, Hunter DJ, Cramer DW, Colditz GA, Speizer FE, Willett WC, et al. Prospective study of talc use and ovarian cancer. J Natl Cancer Inst 2000;92:249–52.
15. Houghton SC, Reeves KW, Hankinson SE, Crawford L, Lane D, Wactawski-Wende J, et al. Perineal powder use and risk of ovarian cancer. J Natl Cancer Inst 2014:106. doi: 10.1093/jnci/dju208.
16. Penninkilampi R, Eslick GD. Perineal talc use and ovarian cancer: a systematic review and meta-analysis. Epidemiology 2018;29:41–9.
17. Deza G, Gimenez-Arnau AM. Allergic contact dermatitis in preservatives: current standing and future options. Curr Opin Allergy Clin Immunol 2017;17:263–8.
18. Branch F, Woodruff TJ, Mitro SD, Zota AR. Vaginal douching and racial/ethnic disparities in phthalates exposures among reproductive-aged women: National Health and Nutrition Examination Survey 2001–2004. Environ Health 2015;14:57.
19. Wormuth M, Scheringer M, Vollenweider M, Hungerbuhler K. What are the sources of exposure to eight frequently used phthalic acid esters in Europeans? Risk Anal 2006;26:803–24.
20. Koniecki D, Wang R, Moody RP, Zhu J. Phthalates in cosmetic and personal care products: concentrations and possible dermal exposure. Environ Res 2011;111:329–36.
21. Parlett LE, Calafat AM, Swan SH. Women's exposure to phthalates in relation to use of personal care products. J Expo Sci Environ Epidemiol 2013;23:197–206.
22. Romero-Franco M, Hernandez-Ramirez RU, Calafat AM, Cebrian ME, Needham LL, Teitelbaum S, et al. Personal care product use and urinary levels of phthalate metabolites in Mexican women. Environ Int 2011;37:867–71.

EXHIBIT 13

EDITORIAL

Use of Powder in the Genital Area and Ovarian Cancer Risk
Examining the Evidence

Dana R. Gossett, MD, MSCI; Marcela G. del Carmen, MD, MPH

Women have used powders for genital hygiene for decades to absorb odor and moisture. While rates of powder use in the genital area have declined over the last 50 years,[1] it remains a routine practice for some women. Commonly used products typically include talc, cornstarch, or some combination of both. Women may apply powders directly to the perineum or onto sanitary napkins, tampons, diaphragms, or underwear. Investigations of an association between the use of talc-containing powders for genital hygiene and epithelial ovarian cancer risks have provided inconsistent results to date and resulted in ongoing controversy. Since 1971, peer-reviewed articles have documented the possible association between talc use and the development of ovarian cancer. However, a PubMed search covering the last 5 decades identified only 17 primary or secondary studies and 36 other articles that were reviews, commentaries, meta-analyses, or letters to the editor.[1-4] In short, while some investigations have been reported, the majority of publications were opinion and discussion articles.

Related article page 49

Several case-control studies identified an increased risk of ovarian cancer with relatively small effect sizes—odds ratios (ORs) of 1.24 to 1.6.[5-8] In a 2018 meta-analysis that included 24 case-control studies and 3 cohort studies, any use of talc in the perineal region was associated with an increased risk of developing epithelial ovarian cancer, with a statistically significant association in case-control studies (OR, 1.35 [95% CI, 1.27-1.43]), and a non-statistically significant association in cohort studies (OR, 1.06 [95% CI, 0.90-1.25]).[2] These studies have been criticized for likely recall bias among patients with cancer, which could increase reported talc use among these patients compared with controls and inflate the calculated association. Cohort studies, such as the Women's Health Initiative (WHI), have not demonstrated the same associations between talc use and ovarian cancer.[9] Since a minority of women in the United States use powder in the genital area, these studies may have lacked power to detect a true association given the relative rarity of epithelial ovarian cancer. Despite this lack of consistency in the primary literature, review articles cited "the robustness of the association between perineal exposure to talc and ovarian cancer."[10-13]

This lack of clarity, as well as recent high-profile litigation regarding the risks of ovarian cancer among users of talc products, prompted O'Brien and colleagues to investigate the question with a larger study population, as reported in this issue of *JAMA*.[14] The authors conducted a pooled analysis of 4 large prospective cohort studies—the Nurses' Health Study (NHS), Nurses' Health Study II (NHSII), Women's Health Initiative Observational Study (WHI-OS), and the Sister Study (SIS). Investigators from 3 of these 4 cohort studies had previously published findings regarding talc use and ovarian cancer risk.[9,15,16] The authors pooled data from all 4 studies to create a cohort of more than 252 745 women, of whom 2168 developed ovarian cancer during the study periods. This is the largest reported investigation to date.

Each of the 4 studies used slightly different measures for powder or talc exposure; 3 of the 4 queried women about duration of use (NHSII, SIS, WHI-OS), and 3 of the 4 queried women about frequency of use (NHS, NHSII, SIS). Thus, the authors of the current investigation performed 2 different dose-response analyses with these 2 subgroups of study participants, one for duration and the other for frequency. The authors identified a decrease in use of powder in the genital area over time, with the oldest cohort (the WHI-OS participants) most likely to report use of powder (53%) and younger participants reporting lower rates of use (NHSII, 26% and SIS, 27%).

Given the varying ages of the participants and the varying duration of exposure and follow-up, the investigators calculated an estimated risk of ovarian cancer by the age of 70 in both the exposed and unexposed groups and found a hazard ratio (HR) of 1.08 (95% CI, 0.99-1.17) between ever users and never users of powder in the genital area. This estimate did not reach statistical significance, although it is important to note the CIs. Examination of duration and frequency of powder use in the genital area yielded similar results, with no evidence of a significant dose-response relationship identified in the study population. However, when the analysis was restricted to women with patent reproductive tracts (in situ uterus and fallopian tubes), the HR among ever users of powder was 1.13 (95% CI, 1.01-1.26). For "frequent" use of powder in the genital area vs non-use among women with patent reproductive tracts, the HR was 1.19 (95%CI, 1.03-1.37; *P* value for trend = .03).

The putative etiologic mechanism for talc as a causative agent in epithelial ovarian cancer is via uptake into the vagina, through the cervix and uterus, and through the fallopian tubes into the peritoneal cavity. The evidence of talc in ovarian specimens lends credence to a transgenital transit mechanism.[17-19] Once in contact with the fallopian tubes, ovaries, and peritoneum, it is posited that talc causes local inflammation and triggers a carcinogenic process.[20] Talc has structural similarities to asbestos and is often found in the same mines from which asbestos is obtained. Whether inflammation occurs in response to mineral talc alone or occurs only when talc is contaminated with asbestos remains

an area of controversy. Data regarding rates of asbestos contamination in talc products are scarce and there are public accusations that companies manufacturing talc powder have manipulated or hidden such data.[21,22] Whether the carcinogenic agent is hypothesized to be talc or asbestos, in either case, the agent would need direct access to the fallopian tubes, ovaries, and peritoneum. Thus, the patency of the reproductive tract during the time of exposure is of paramount interest. If a woman has had a hysterectomy or a tubal ligation, then talc applied to the vulva or vagina will have no means of ingress and could not cause inflammation of the fallopian tubes or ovaries.

Given this putative mechanism of exposure, the subgroup analysis of women with patent reproductive tracts is of particular interest. However, it is not possible to equate a patent reproductive tract with exposure and a nonpatent reproductive tract with nonexposure. Women who undergo tubal ligation or hysterectomy (nonpatent) and use powders in the genital area cannot be assumed to have started using them only after their surgeries—in fact, this is highly unlikely as women often begin use of powder in the genital area during adolescence. Thus, the stratification of the groups as patent and nonpatent does not clearly group women into exposed and nonexposed categories. The fact that there are no significant differences in the HRs in the patent (HR, 1.13 [95% CI, 1.01-1.26]) and nonpatent subgroups (HR, 0.99 [95% CI, 0.86-1.15]; *P* value for heterogeneity comparing these subgroups of .15) confirms the overall conclusion that there is no demonstrable statistically significant association between use of powder in the genital area and ovarian cancer risk. This is the key finding of the study. The subgroup analysis suggesting that women with intact reproductive tracts who used powder in the perineal area developed ovarian cancer more frequently than nonusers is below the effect size that epidemiologists generally consider important and should not be selectively highlighted by the statistically unsophisticated reader as evidence of a relationship. In addition, the investigators conducted multiple subgroup analyses increasing the risk of a type I error or a finding that reaches statistical significance but results from chance alone. The fact that this subgroup finding barely achieves statistical significance is further evidence that it is does not represent a true association. The conclusions of the authors, supported by tests of heterogeneity across subgroup HRs, are that there was no evidence of a statistically significant association between use of powder in the genital area and ovarian cancer.

The study by O'Brien et al represents the largest cohort to date to examine whether an association exists between powder use in the genital area and ovarian cancer risk, and the findings are overall reassuring. Yet, despite 3.8 million person-years of observation in the study population, the number of ovarian cancer cases was small, and it is possible that the study was underpowered to detect small increases or decreases in ovarian cancer rates. Future analyses would be strengthened by focusing on women with intact reproductive tracts, with particular attention to timing and duration of exposure to powder in the genital area. Accumulation of such data will take many years, and given the low rates of current powder use among US women, may not be feasible. Nonetheless, the rigorously conducted study by O'Brien et al contributes important and timely data about the potential link between use of powder in the genital area and risk of ovarian cancer.

ARTICLE INFORMATION

Author Affiliations: Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco (Gossett); Department of Obstetrics, Gynecology, and Reproductive Biology, Harvard University Medical School, Boston, Massachusetts (del Carmen).

Corresponding Author: Dana R. Gossett, MD, MSCI, Department of Obstetrics, Gynecology, and Reproductive Sciences, University of California, San Francisco, 2356 Sutter St, J-140, San Francisco, CA 94611 (dana.gossett@ucsf.edu).

Conflict of Interest Disclosures: Dr Gossett reports receipt of other from Bayer for expert consultancy services (Mirena intrauterine device) outside the submitted work. No additional disclosures were reported.

REFERENCES

1. Narod SA. Talc and ovarian cancer. *Gynecol Oncol*. 2016;141(3):410-412. doi:10.1016/j.ygyno.2016.04.011

2. Penninkilampi R, Eslick GD. Perineal talc use and ovarian cancer: a systematic review and meta-analysis. *Epidemiology*. 2018;29(1):41-49. doi:10.1097/EDE.0000000000000745

3. Berge W, Mundt K, Luu H, Boffetta P. Genital use of talc and risk of ovarian cancer: a meta-analysis. *Eur J Cancer Prev*. 2018;27(3):248-257. doi:10.1097/CEJ.0000000000000340

4. Wentzensen N, Wacholder S. Talc use and ovarian cancer: epidemiology between a rock and a hard place. *J Natl Cancer Inst*. 2014;106(9):dju260. doi:10.1093/jnci/dju260

5. Terry KL, Karageorgi S, Shvetsov YB, et al; Australian Cancer Study (Ovarian Cancer); Australian Ovarian Cancer Study Group; Ovarian Cancer Association Consortium. Genital powder use and risk of ovarian cancer: a pooled analysis of 8525 cases and 9859 controls. *Cancer Prev Res (Phila)*. 2013;6(8):811-821. doi:10.1158/1940-6207.CAPR-13-0037

6. Cramer DW, Vitonis AF, Terry KL, Welch WR, Titus LJ. The association between talc use and ovarian cancer: a retrospective case-control study in two US states. *Epidemiology*. 2016;27(3):334-346. doi:10.1097/EDE.0000000000000434

7. Mills PK, Riordan DG, Cress RD, Young HA. Perineal talc exposure and epithelial ovarian cancer risk in the Central Valley of California. *Int J Cancer*. 2004;112(3):458-464. doi:10.1002/ijc.20434

8. Cook LS, Kamb ML, Weiss NS. Perineal powder exposure and the risk of ovarian cancer. *Am J Epidemiol*. 1997;145(5):459-465. doi:10.1093/oxfordjournals.aje.a009128

9. Houghton SC, Reeves KW, Hankinson SE, et al. Perineal powder use and risk of ovarian cancer. *J Natl Cancer Inst*. 2014;106(9):dju208. doi:10.1093/jnci/dju208

10. Daly M, Obrams GI. Epidemiology and risk assessment for ovarian cancer. *Semin Oncol*. 1998;25(3):255-264.

11. Cramer DW. The epidemiology of endometrial and ovarian cancer. *Hematol Oncol Clin North Am*. 2012;26(1):1-12. doi:10.1016/j.hoc.2011.10.009

12. Hunn J, Rodriguez GC. Ovarian cancer: etiology, risk factors, and epidemiology. *Clin Obstet Gynecol*. 2012;55(1):3-23. doi:10.1097/GRF.0b013e31824b4611

13. Kadry Taher M, Farhat N, Karyakina NA, et al. Critical review of the association between perineal use of talc powder and risk of ovarian cancer. *Reprod Toxicol*. 2019;90:88-101. doi:10.1016/j.reprotox.2019.08.015

14. O'Brien KM, Tworoger SS, Harris HR, et al. Association of powder use in the genital area with risk of ovarian cancer [published January 7, 2020]. *JAMA*. doi:10.1001/jama.2019.20079

15. Gertig DM, Hunter DJ, Cramer DW, et al. Prospective study of talc use and ovarian cancer. *J Natl Cancer Inst*. 2000;92(3):249-252. doi:10.1093/jnci/92.3.249

16. Gonzalez NL, O'Brien KM, D'Aloisio AA, Sandler DP, Weinberg CR. Douching, talc use, and risk of ovarian cancer. *Epidemiology*. 2016;27(6):797-802. doi:10.1097/EDE.0000000000000528

17. Henderson WJ, Hamilton TC, Griffiths K. Talc in normal and malignant ovarian tissue. *Lancet*. 1979;1(8114):499. doi:10.1016/S0140-6736(79)90860-2

18. Cramer DW, Welch WR, Berkowitz RS, Godleski JJ. Presence of talc in pelvic lymph nodes of a woman with ovarian cancer and long-term genital exposure to cosmetic talc. *Obstet Gynecol*. 2007;110(2 pt 2):498-501. doi:10.1097/01.AOG.0000262902.80861.a0

19. Heller DS, Westhoff C, Gordon RE Katz N. The relationship between perineal cosmetic talc usage and ovarian talc particle burden. *Am J Obstet Gynecol*. 1996; 174(5): 1507-1510. doi:10.1016/s0002-9378(96)70597-5

20. Buz'Zard AR, Lau BH. Pycnogenol reduces talc-induced neoplastic transformation in human ovarian cell cultures. *Phytother Res*. 2007;21(6):579-586. doi:10.1002/ptr.2117

21. Rosner D, Markowitz G, Chowkwanyun M. "Nondetected": the politics of measurement of asbestos in talc, 1971-1976. *Am J Public Health*. 2019;109(7):969-974. doi:10.2105/AJPH.2019.305085

22. Rabin RC, Hsu T. Johnson & Johnson feared baby powder's possible asbestos link for years. *New York Times*. December 14, 2018. https://www.nytimes.com/2018/12/14/business/baby-powder-asbestos-johnson-johnson.html. Accessed December 2, 2019.

Can an Evidence-Based Approach Improve the Patient-Physician Relationship?

Adam S. Cifu, MD; Anthony Lembo, MD; Andrew M. Davis, MD, MPH

The importance of the patient-physician relationship has been recognized for millennia.[1,2] Concern that this special relationship is threatened has likely existed nearly as long, although more recently time constraints, insurer demands, novel technologies, and documentation burdens have intensified these worries.[3,4] In their Special Communication in this issue of *JAMA*, Zulman et al report a novel study that proposes a limited number of evidence-based practices that may lead to more meaningful connections between patients and physicians.[5]

Editorial page 33

Related article page 70 and Audio and Video

The novelty of this study is the approach the authors used to identify, group, and distill their suggested practices. The authors first performed a literature search that identified 73 studies of evidence-based, interpersonal interventions that could potentially improve practice in 4 domains: patient experience, clinician experience, population health, and health care utilization and cost. Next, a diverse group of physicians, chosen for their exceptional interpersonal skills, were observed in 27 distinct patient encounters. Patients and physicians were debriefed after the interview to identify successful strategies used by the clinicians. Then, nonmedical professionals from 7 professions whose jobs involve intense interpersonal interactions were interviewed to identify cross-disciplinary practices thought to foster human connection.

Through these steps, the research team identified potentially useful clinical approaches that were perceived to contribute to physician "presence," defined by the authors as a purposeful practice of "awareness, focus, and attention with the intent to understand and connect with patients." These practices were rated by patients and clinicians on their likely effects and feasibility in practice. A Delphi process was used to condense 13 preliminary practices into 5 final recommendations, which were (1) prepare with intention, (2) listen intently and completely, (3) agree on what matters most, (4) connect with the patient's story, and (5) explore emotional cues. Each of these practices is complex, and the authors provide detailed explanations, including narrative examples and links to outcomes, that are summarized in the article and included in more detail in the online supplemental material.

If implemented in practice, these 5 practices suggested by Zulman and colleagues are likely to enhance patient-physician relationships, which ideally could help improve physician satisfaction and well-being, reduce physician frustration, improve clinical outcomes, and reduce health care costs. Importantly, the authors also call for system-level interventions to create an environment for the implementation of these practices. Although the patient-physician interaction is at the core of most physicians' activities and has led to an entire genre of literature and television programs, very little is actually known about what makes for an effective relationship. In part, this is because the patient-physician interaction occurs in private, making its study difficult.[6] Efforts to identify effective practices, measure their effectiveness, and learn to teach them are uncommon. The authors' methods of searching for strategies that have some evidentiary support, enhancing their search with clinical experiences and nonclinical expertise, and then synthesizing this information into potentially usable strategies are impressive. They also emphasize the importance of culturally sensitive care and caution against assumptions based on race, ethnicity, gender, socioeconomic status, or past encounters.

However, there are challenges in considering the results of the study. One reason might be the lack of a clear connection between the evidence and the recommendations. A report that focused on motivational interviewing in nursing practice was used to bolster the recommendation to "connect with the patient's story."[7] While the advice to prepare and listen to a patient would be advised by most practicing clinicians without reading this Special Communication, "listen intently and completely" and "explore emotional cues" are such broad and generic recommendations that physicians might as well be advised to be attentive and kind.

The recommendations are on strongest ground in linking the 5 recommended practices to the domains of improved patient and clinician satisfaction. It is less clear if following the recommended practices will actually lead to improved clinical outcomes. For example, in support of the "explore emotional cues" recommendation, Zulman et al cited the "population health" benefit of a study that showed an association between an intervention enhancing clinician empathy and a reduction of common cold symptoms from 7 days to 5.9 days.[8]

EXHIBIT 14

Gynecologic Oncology 163 (2021) 199–208

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Invited Review

Talc, body powder, and ovarian cancer: A summary of the epidemiologic evidence

Nicolas Wentzensen [a,*], Katie M. O'Brien [b]

[a] Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Rockville, MD, United States of America
[b] Epidemiology Branch, National Institute of Environmental Health Sciences, Research Triangle Park, NC, United States of America

HIGHLIGHTS

- Genital powder use shows a weak association with ovarian cancer risk.
- The increase in absolute risk of ovarian cancer is very small.
- Body powders have different ingredients that can be hard to quantify.
- The causal mechanism underlying the observed associations is not clear.

ARTICLE INFO

Article history:
Received 11 April 2021
Received in revised form 19 July 2021
Accepted 21 July 2021
Available online 6 August 2021

Keywords:
Talc
Ovarian cancer
Genital powder
Uterine cancer
Bias
Confounding

ABSTRACT

Many women apply powder to the genital area as a drying agent. Talc, an inert mineral with a high capacity to absorb water, has historically been a major component of body powders. Due to its similarity and co-occurrence with asbestos, the association of body powder/talc use and gynecological cancer risk, specifically ovarian cancer risk, has been a long-standing research question. Retrospective case-control studies have shown associations between genital powder use and ovarian cancer risk, with summary relative risk estimates from meta-analyses and pooled analyses ranging from 1.24 to 1.35 for ever versus never use. In contrast, prospective cohort studies have not shown a statistically significant association until recently, when a pooled analysis of four large cohorts demonstrated a weak, but statistically significant association among women with patent reproductive tracts (hazard ratio 1.13). Taken together, the epidemiological data from case-control studies and cohort studies suggest that there may be a small, positive association between genital powder use and ovarian cancer. The causal factors underlying this association are not clear. Proposed factors include talc, other minerals, such as asbestos or quartz, that are known carcinogens and may contaminate talc products, or other powder ingredients that could cause inflammation of the reproductive tracts. Given the rarity of ovarian cancer in the general population, the small increase in relative risk translates to a very low increase in absolute risk. Further research is needed to understand the underpinnings of the observed association between genital powder use and ovarian cancer risk.

Contents

* Corresponding author at: Division of Cancer Epidemiology and Genetics, National Cancer Institute, 9609 Medical Center Drive, Room 6E-448, Bethesda, MD 20892-9774, United States of America.
E-mail address: wentzenn@mail.nih.gov (N. Wentzensen).

https://doi.org/10.1016/j.ygyno.2021.07.032
0090-8258/

1. Introduction

Talc is a soft and inert mineral with a high capability to absorb water and organic matter. It is used in a wide range of products, including paper, plastics, paint, rubber, agricultural products, pharmaceuticals, and cosmetics [1]. Because of its capacity to bind water, talc powder has been used in baby powders and feminine hygiene products as a drying agent. Notably, talc shares chemical features and often co-occurs with asbestos, a long-established carcinogen [2]. Due to the similarity with asbestos, talc has been evaluated for its carcinogenic potential [1]. Powder application to the genital area has been fairly common, but body powders contain varying levels of talc, including some labeled as talc-free [3]. Historically, there has been great interest in whether there is a link between genital talc use and cancers of the female reproductive tract.

The assessment of the carcinogenic potential of a biological or chemical agent is based on multiple lines of evidence from diverse studies, including epidemiological studies, mechanistic studies, cancer bioassays, and animal experiments. This review focuses on epidemiological data, particularly on studies evaluating the association between body powder/talc and ovarian cancer.

In 1971, Henderson et al. showed talc particles in 10 out of 13 ovarian cancer tissue samples, as well as in a low number of endometrial and cervical cancer tissues [4]. In 1979, Longo and Young summarized the evidence available at the time for a role of talc in ovarian cancer and laid out what studies would be needed to better assess the relationship [5]. In 1982, Cramer et al. published the first epidemiological study evaluating the association between genital talc use and ovarian cancer [6]. In a case-control study conducted in the Boston area, the authors reported an increased risk of ovarian cancer (OR 1.92; 95% CI 1.27–2.89) for any perineal exposure to talc. Since then, several case-control studies evaluating the association between talc or body powder and ovarian cancer have been published that showed positive associations, while evaluations in prospective cohort studies have shown only weak or no associations (summarized in Table 1). Associations between talc use and uterine cancer have also been investigated in several case-control and cohort studies.

In 2010, IARC published volume 93 of their Monograph series on "Evaluation of Carcinogenic Risks to Humans" that included the assessment of carcinogenicity of carbon black, titanium dioxide, and talc [1]. Based on the summary of the biological and epidemiological data at the time, the IARC group classified talc as a possible carcinogen (2B), which means that there is some evidence that a substance can cause cancer in humans, but that the evidence was not conclusive. Since the 2010 IARC carcinogenicity assessment, several epidemiological studies have been published that expand the state of knowledge about talc's possible carcinogenicity. In this review, we evaluate the epidemiological evidence on whether there is an association between body powder use and ovarian cancer risk. If the evidence suggests an association between powder use and ovarian cancer, it is important to understand underlying causal factors and the potential clinical and public health relevance.

2. Chemical properties of talc in body powder

Talc may either refer to mineral talc itself, or to cosmetic products that contain mineral talc in varying proportions, often in combination with corn starch. Talc is a metamorphic mineral composed of magnesium silicate (generalized chemical formula $Mg_3Si_4O_{10}(OH)_2$). Mineral talc is commonly platy, i.e. it occurs in flaky layers or sheets, but it can also occur as asbestiform fibers. Talc is the softest known mineral. Solid talc minerals are crushed into a white powder referred to as talcum powder that has great ability to absorb both watery and oily substances. This form of talc is the focus of the current review.

Talc can be contaminated with a variety of other minerals. Most important are contaminations with asbestos or quartz, both class 1 carcinogens according to IARC (which means that there is enough evidence to conclude that these substances can cause cancer in humans), which frequently co-occur naturally with talc [7]. Early cosmetic talc products were found to be contaminated with asbestos to various extent [8]. More stringent quality control introduced in talc production in 1976 led to a steep reduction in asbestos contamination. While talc products since the 1980s have been considered asbestos-free, recent reports have suggested that low-level contamination of talc with asbestos fibers may have persisted in some cosmetic products. To systematically assess the presence of asbestos in cosmetic products, the US FDA recently conducted extensive testing of cosmetic talc products and identified several products with asbestos contaminations that have subsequently been recalled from the market [9]. It cannot be excluded that other ingredients of body powders, such as corn starch, may also have biological effects, e.g. by causing irritation or inflammation of the female reproductive tract.

3. Biological properties of talc and carcinogenicity studies

The number of biologic and animal studies evaluating the carcinogenic potential of talc is limited. In autopsy studies, talc particles have been found in the lungs of occupationally exposed individuals [10]. Pathology studies have shown talc particles in various cancer tissues including stomach tumors and gynecological tumors, suggesting that talc can reach various parts of the body through inhalation, deposition, and even retrograde movement in the female genital tract [1]. Potential toxic effects of talc may depend on the route and dose of administration. When conducting carcinogenicity assessment, it is important to distinguish effects caused by other contaminating minerals such as asbestos or quartz, from talc-specific effects. This distinction is only possible when highly pure substances are studied.

The carcinogenicity of talc has been evaluated in few animal studies, summarized in the IARC monograph [1]. For example, mice were

Table 1
Reported estimates of the association between ever (versus never) powder use and ovarian cancer, including summary estimates from published meta- and pooled analyses.

Author	Year	OR (95% CI)	Meta-analyses			Pooled analyses			Comments
			Penninkilampi 2018	Berge 2018	Taher 2019	Terry 2013	O'Brien 2020[a]	Davis 2021[b]	
Overall summary estimates			1.31 (1.24–1.39)	1.22 (1.13–1.3)	1.28 (1.2–1.37)	1.24 (1.15–1.33)	1.08 (0.99–1.17)	1.32 (1.17–1.48)[c]	
Case control summary estimates			1.35 (1.27–1.43)	1.26 (1.17–1.35)	1.32 (1.24–1.40)	1.24 (1.15–1.33)			
Cramer	1982	1.92 (1.27–2.89)	X	X	X				
Hartge	1983	2.5 (0.7–10)	X	X	X				Meta-analyses used different subgroup estimates
Whittemore	1988	1.4 (1.98–2)	X	X	X				
Booth	1989	1.3 (0.94–1.8)	X	X					
Harlow	1989	1.1 (0.7–2.1)	X	X	X				
Chen	1992	3.9 (0.9–10.6)	X	X					
Harlow	1992	1.5 (1–2.1)		X	X				
Rosenblatt	1992	1 (0.2–4)	X	X	X				Meta-analyses used different subgroup estimates
Tzonou	1993	1.05 (0.28–3.98)	X	X	X				
Purdie	1995	1.27 (1.04–1.54)	X	X					
Shushan	1996	2 (1.11–3.6)	X						
Green	1997	1.3 (1.06–1.6)	X		X				
Chang	1997	1.42 (1.08–1.86)	X	X	X	X			
Cook	1997	1.5 (1.1–2)	X	X	X				
Godard	1998	2.49 (0.94–6.6)	X	X	X				
Wong	1999	0.92 (0.24–3.57)	X	X	X				
Ness	2000	1.5 (1.1–2)	X	X	X				
Mills	2004	1.37 (1.02–1.85)	X	X	X				
Goodman	2008	0.99 (0.7–1.41)		X		X			Abstracted numbers from Terry 2013
Merritt	2008	1.17 (1.01–1.36)	X	X	X	X			
Gates	2008	1.06 (0.89–1.28)			X				Data updated by Gates 2010 and Cramer 2016
Moorman	2009	1.37 (1.05–1.8)		X	X	X		X	Abstracted numbers from Terry 2013
Rosenblatt	2011	1.27 (0.97–1.66)	X	X	X	X			
Lo-Ciganic	2012	1.34 (1.07–1.66)		X		X			Abstracted numbers from Terry 2013
Kurta	2012	1.4 (1.16–1.69)	X		X				
Wu	2015	1.46 (1.27–1.69)	X	X	X	X		X	
Cramer	2016	1.33 (1.16–1.52)	X	X	X	X			Update of Gates 2010
Schildkraut	2016	1.44 (1.11–1.86)	X	X	X			X	
Cohort summary estimates			1.06 (0.9–1.25)	1.02 (0.85–1.2)	1.06 (0.9–1.25)		1.08 (0.99–1.17)		
Gertig	2000	1.09 (0.86–1.38)	X		X		X		Updated in Gates 2010, updated numbers in O'Brien 2020
Gates	2010	1.06 (0.89–1.28)		X			X		
Houghton	2014	1.12 (0.92–1.36)	X	X	X		X	X	Updated numbers in O'Brien 2020
Gonzalez	2016	0.73 (0.44–1.21)	X	X	X		X		Updated numbers in O'Brien 2020

[a] Additionally includes data from the Nurses' Health Study II (talc data unpublished)
[b] Additionally includes data from the Cook County Case-Control Study (talc data previously unpublished).
[c] OR = 1.22 (95% CI: 0.97–1.53) in African-American women; OR = 1.36 (95% CI: 1.19–1.57) in White women.

subjected to inhalation, as well as subcutaneous, intraperitoneal, and intrathoracic injection. Generally, no increase in tumor incidence was observed in mice. Rats were subjected to oral administration, inhalation, as well as intraperitoneal, intrathoracic, or intrapleural injection, and ovarian implantation. In some studies, incidences of alveolar and bronchial carcinomas were increased after talc inhalation. An increase in pheochromocytomas was also observed, but the IARC group did not consider that pheochromocytomas are causally related to talc. Hamsters were subjected to inhalation and intratracheal injection; no tumors were observed in these studies. A study conducted in rats that evaluated intravaginal and perineal talc application did not observe any neoplastic changes, but inflammatory reactions in the fallopian tubes and other areas of the genital tract [11]. However, the limited follow-up time may have precluded development of tumor endpoints.

Several lines of evidence suggest that talc causes inflammatory reactions. Animal studies have shown release of cytokines, chemokines and growth factors from pleural mesothelial cells after injection with talc. Similarly, in human tissue, intrapleural talc injection has led to inflammation and pleural fibrosis. In patients with documented perineal talc use, talc particles can be found in multiple sites along the female reproductive tract [12]. Talc use was shown to have an inverse association with MUC1 antibodies in healthy women, but the biologic process underlying this association is not understood [13]. One study found a higher risk of ovarian cancer associated with powder use among women with variations in the GSTM1 and GSTT1 genes [14], but to our knowledge, no other studies have examined potential gene-by-environment interactions.

4. Important considerations for epidemiological studies of talc use and gynecological cancer risk

4.1. Etiologic heterogeneity of ovarian cancer

Ovarian cancer is characterized by profound heterogeneity that can be observed in site of origin, genetic susceptibility, somatic mutations, molecular pathways, risk factor associations and morphologic differences [15–17]. In aggregate, these data suggest that there are several etiologically distinct types of cancers that manifest in the ovaries. It has been proposed that a majority of high-grade serous carcinomas arise from the fallopian tubes, while endometrioid carcinomas may arise from orthotopic or ectopic endometrial tissue, including endometriosis tissue [15]. Many ovarian cancer risk factors and exposures are specific to certain subtypes [16]. Demonstrating a subtype-specific association can, theoretically, point to a specific carcinogenic effect.

Further, there is similarity between subtypes of ovarian and endometrial cancers [18]. Serous ovarian and endometrial carcinomas have similar molecular features and may originate from the same cells in the fallopian tube. Similarly, endometrioid ovarian carcinomas share risk factors and molecular features with endometrioid endometrial carcinomas [16,19,20]. Therefore, comparisons of subtype-specific associations across gynecologic cancer sites can inform the carcinogenic process.

4.2. Study designs

Epidemiological studies of talc exposure have been conducted in special populations, like talc miners and pulp and paper industry workers who are exposed to high doses of talc over an extended time period. These occupational studies allow for the assessment of very high levels of exposure that are typically not found in the general population, with possibilities for detailed studies of dose-response effects (duration and frequency). However, due to the possible contamination of talc with co-existing minerals in mines and in industrial talc products, evaluating talc-specific effects remains a challenge. Ovarian cancer is particularly difficult to study in occupational settings, as high-exposure jobs are typically male-dominated.

In the general population, epidemiological studies of talc use and gynecological cancer risk include case-control studies and prospective cohort studies. A case-control study is an observational study consisting of a group of cases who experienced a specific outcome, such as ovarian cancer, as well as controls without that outcome [21,22]. These are compared to see if there are differences in exposure patterns between the two groups. Controls for case-control studies should be sampled from the base population from which the cases arise. Incompatibility between the controls and the true source population can lead to bias, as discussed further below. In contrast, cohort studies are observational studies that follow an initially non-diseased population to see who develops the outcome(s) of interest [23]. Cohort studies are typically much larger than case-control studies and require long-term follow-up, especially for rare outcomes.

These study designs have different advantages and disadvantages. The major difference between case-control studies and cohort studies is that case-control studies assess exposures at the time of or just after a cancer diagnosis, which can lead to differential reporting of exposures by cases and controls. In contrast, exposure assessment in cohort studies occurs before the cancer diagnosis. Case-control studies typically focus on a single disease of interest, like ovarian cancer, and are specifically designed to evaluate the exposures of interest for that specific disease. Therefore, case-control studies tend to have more detailed information on specific exposures. In contrast, cohort studies generally evaluate a wide range of disease outcomes. Exposure assessment is much broader and usually does not go as deep into specific exposures. For genital powders, this means studies will typically have less information on mode of application, dose, and duration. Further, when exposure assessment is not re-assessed at later follow-up times in cohort studies, the exposure assessment may refer to a time period that was many years, if not decades, prior to disease development, thereby opening the possibility to non-differential misclassification.

For rare diseases, cohort studies must be of sufficient size and duration to allow for well-powered assessment of potential risk factors. Most individual prospective cohort studies have not observed meaningful associations between talc use and ovarian cancer risk. However, many cohort studies have few cases and may not be sufficiently powered to detect a small increase in risk at statistically significant levels. It is important to be transparent about study power and the lower limit of detectable associations when reporting study results.

Both case-control studies and cohort studies typically report relative risk measures, including odds ratios or hazard ratios. These relative risks indicate how much the risk of an outcome is increased due to a specific exposure in one group compared to another. Measures of absolute risk of disease may have greater clinical relevance but are often difficult to assess using these standard study designs. Disease prevalence is a key factor here: the rarer the disease, the smaller the absolute risk increase for a given relative risk increase [24]. Accordingly, for a rare disease like ovarian cancer, even a large relative increase may not translate to an increase in absolute risk that is considered clinically meaningful.

4.3. Bias and confounding

In contrast to randomized trials, which are designed to achieve unbiased assessment of specific exposures, drugs, or interventions, observational studies are at risk of bias. In epidemiology, bias is defined as an error in the study design or conduct that leads to results that are systematically different from the truth [25]. Key forms of bias including selection bias, information bias, and confounding. Selection bias is introduced when there is a systematic difference between study participants and the base population, or a systematic difference between cases and non-cases. Information bias may occur when data on exposure or outcomes is systematically different between cases and non-cases. This includes recall bias, discussed in further detail below, and survivor bias, which could occur if talc use affected survival time. Survivor bias is a potentially important source of bias for retrospective studies of diseases with high fatality rates, such as ovarian cancer, as cases need to live long enough to be included. If cases are not interviewed soon after their diagnosis, the sample may include a disproportionate number of women with less severe disease.

Confounding occurs when an exposure is associated with an outcome, but the causal association is driven by a different factor that is correlated with both the exposure and the outcome. If the confounding factor is well-measured, bias due to confounding can be mitigated by adjusting for or stratifying on that variable using multivariable regression models. As an example, the association between genital powder use and uterine cancer is strongly confounded by body mass index (BMI), which is both a risk factor for uterine cancer and a strong predictor of genital powder use. As shown by O'Brien et al., while crude estimates of the genital powder use- uterine cancer relationship indicated a strong positive association, models adjusted for BMI indicated there was no independent relationship between body powder use and uterine cancer [26].

4.4. Assessment and quantification of talc exposure

Since talc use is not documented in medical or pharmacy records, assessment of talc exposure relies purely on self-report [27]. Cosmetic talc products are typically not easily recognizable without studying the list of ingredients. Body powders have a wide range of ingredients with different talc content, including some talc-free varieties. Since many study participants may not know whether they used talc, questionnaires in epidemiologic studies often ask about body powder use. Some case-control studies include questions about the mode of application. Body

powder may be applied to the genital area directly or via application to sanitary napkins or diaphragms [1].

When evaluating associations between exposures and disease outcomes in epidemiological studies, establishing a dose-response relationship can be important to support a causal association. Due to the varying talc content of body powders and the different modes of application, it is difficult to estimate the actual talc dose applied to the genital area.

Despite these limitations, some case-control studies have assessed the frequency and duration of genital powder use. This allows researchers to distinguish groups with potentially higher and lower exposure, even when the absolute talc exposure level cannot be quantified. Cohort studies typically have collected less information on dose and frequency of application than case-control studies.

4.5. Recall bias

Since exposure assessment in case-control studies is conducted at the time of diagnosis, there is a risk of differential recall bias, a type of information bias. This occurs when reporting of an exposure is influenced by the diagnosis and affected individuals are more likely to report a specific exposure or are likely to report a higher dose or duration of exposure compared to control individuals. This differential recall bias may result in an association of an exposure with disease outcome when there is truly none, or it may lead to overestimation of a truly small association.

Differential recall bias has been observed in case control studies for a wide range of exposures, but there are specific and well-documented concerns that differential recall bias underlies some of the associations in case-control studies of talc use and ovarian cancer risk. For example, in a large case-control study of African American women conducted in North Carolina Schildkraut et al. reported a strong association between talc use and ovarian cancer [28,29]. However, they only observed a significant association between genital powder use and ovarian cancer in participants interviewed after 2014 (adjusted OR, 2.91; 95% CI, 1.70–4.97), a benchmark for when a possible talc–ovarian cancer association began being widely discussed in the media as a result of ongoing litigation. Prior to 2014, the association was weaker and not statistically significant (OR, 1.19; 95% CI, 0.87–1.63; P interaction by time period = 0.005). Importantly, the prevalence of genital powder use among controls was the same across the two time periods, whereas the proportion of cases reporting "any" genital powder use increased among those interviewed during the later time period. This suggests that differential recall of body powder use may explain at least some of the observed associations.

4.6. Confounding by indication

Confounding by indication is a concern in epidemiological studies evaluating drugs and other exposures. It can occur when an underlying cause of the outcome also causes changes to exposure. An example relevant to the powder-ovarian cancer association is if a hormone-related condition was a risk factor for ovarian cancer, and also altered the vaginal environment in a way that made women more or less likely to apply genital powder. Such a relationship would induce a non-causal association between talc use and ovarian cancer. Most studies do not collect data on the underlying reason for talc use, which may be wide ranging. Without this knowledge, we cannot rule out confounding by indication.

4.7. Timing of exposure

Talc/body powder may be used over a wide age range, or only during a short period in life. The biologic effect of body powder on the cells at risk of ovarian cancer may differ depending on the timing of exposure. With the example of ovarian and other cancers, the disease latency period may be quite long, meaning that use several decades prior could be associated with disease risk. On the other extreme, recent use could also be relevant, including as a promoter of pre-cancerous cells into tumors, or by accelerating the growth of existing tumors. Few studies have collected information on talc/body powder dose and duration during specific time windows or across the lifespan. Depending on how talc/body powder exposure is assessed, many studies may not evaluate the relevant exposure window.

5. Summary of the data for genital powder use and ovarian cancer risk

5.1. Overall associations reported in systematic reviews, meta-analyses, and pooled analyses

Over the last 15 years, several systematic reviews and meta-analyses evaluating the association between body powder or talc use and ovarian cancer have been published. Three recent meta-analyses and three pooled analyses are summarized in Table 1 [30–34]. A total of 32 papers were included in at least one of the meta-analyses and pooled analyses spanning articles from 1982 to 2016 [6,14,28,35–62]. There were some differences with regard to inclusion of studies and specific estimates which resulted in differences of the reported associations between the meta-analyses and the pooled analyses.

Penninkilampi and Eslick summarized 23 case-control studies and 3 cohort studies via meta-analysis [33]. Any perineal talc use was associated with increased risk of ovarian cancer (OR = 1.31; 95% CI: 1.24–1.39). An association with ever use of talc was found in the meta-analysis of case-control studies (OR = 1.35; 95% CI: 1.27–1.43), but not cohort studies (OR = 1.06; 95% CI: 0.90–1.25). The systematic review also evaluated lifetime applications of talc to assess whether there is a dose-response relationship. Subjects with more than 3600 lifetime applications (OR = 1.42; 95% CI: 1.25–1.61) had a slightly higher risk of ovarian cancer compared to those with <3600 applications (OR = 1.32; 95% CI: 1.15–1.50).

Berge et al. summarized 24 case-control studies and 3 cohort studies via meta-analysis [30]. The overall summary relative risk (RR) for ever use of genital talc and ovarian cancer was 1.22 (95% CI: 1.13–1.30). The RR for case-control studies was 1.26 (95% CI: 1.17–1.35) and for cohort studies was 1.02 (95% CI: 0.85–1.20, P-for-heterogeneity by study design = 0.007). There was a weak trend in RR with duration and frequency of genital talc use.

Taher et al. summarized 21 case-control studies and 3 cohort studies [31]. This was the most recently published meta-analysis, and the authors included a detailed comparison of included studies in their supplemental materials, with the main differences being the exclusion of studies that did not report talc use as main effect estimates in their original publication. A positive association between perineal use of talc powder and ovarian cancer was found (OR = 1.28; 95% CI: 1.20–1.37). They noted significant risks in Hispanic and White women, in women applying talc to underwear, in pre-menopausal women, and in post-menopausal women receiving hormonal therapy.

Terry et al. published a large pooled analysis from the Ovarian Cancer Association Consortium (OCAC) [34]. This pooled analysis included eight case-control studies that are included in the previously discussed meta-analyses. In contrast to meta-analyses, pooled analyses make use of the original data, with the ability to harmonize exposure categories and covariates across studies. Based on data from 8525 cases and 9859 controls, Terry et al. found that genital powder use was associated with a statistically significant increase in risk of ovarian cancer (OR = 1.24, 95% CI: 1.15–1.33). There was limited evidence of a dose-response trend across categories of lifetime number of applications (p-for-trend = 0.17).

O'Brien et al. pooled data from the four large prospective cohorts known to have information on genital powder use [32]. This included updated data from three previously published cohorts [14,40,42,48] as well as previously unpublished data from the Nurses' Health Study II. Ever use of genital powder was associated with a small but not

statistically significant increase in ovarian cancer risk (HR = 1.08, 95% CI: 0.99–1.17). There was no evidence that more frequent or long-term use was associated with further increases in risk.

Most recently, Davis et al. published results from a pooled analysis of 5 studies (4 population-based case-control, 1 prospective cohort) participating in the Ovarian Cancer in Women of African Ancestry Consortium (OCWAA) [63]. They observed a positive association between genital powder use and ovarian cancer in both African-American women (OR = 1.22, 95% CI: 0.96–1.55) and White women (OR = 1.34, 95% CI: 1.16–1.56 in White women), with a combined estimate of OR = 1.31 (95% CI: 1.15–1.48) overall. There were no clear dose-response trends.

5.2. Associations of genital powder use and ovarian cancer risk by histotype

As discussed previously, ovarian cancers encompass several different histotypes, which may have different cells of origin and unique risk factors. The identification of subtype-specific associations could strengthen the argument for the existence of a causal relationship. Most studies published since 1997 have included histotype-specific estimates, with serous ovarian cancers (sometimes restricted to high grade serious or invasive serous) being the most common (Table 2). In the previously published meta-analyses, Penninkilampi and Eslick reported that ever talc use was positively associated with serous carcinomas (OR = 1.32, 95% 1.22–1.43), including among cohort studies only (OR = 1.25, 95% CI: 1.01–1.55) [33]. Talc use was also positively associated with endometroid tumors (OR = 1.35, 95% CI: 1.14–1.60), and possibly mucinous (OR = 1.12, 95% CI: 0.94–1.33), but not clear cell (OR = 1.02, 95% CI: 0.75–1.39).

The Berge et al. meta-analysis reported similar findings, including a positive association between talc use and serous carcinoma (RR: 1.24; 95% CI: 1.15–1.34) and to a lesser extent endometroid carcinoma (RR: 1.15, 95% CI: 0.91–1.39), but not mucinous (RR = 0.96, 95% CI:

Table 2
Reported estimates of the association between ever (versus never) powder use and ovarian cancer by histotype, including summary estimates from published meta- and pooled analyses.

Author	Year	Serous	Endometroid	Mucinous	Clear cell	Meta-analyses			Pooled analyses		
						Penninkilampi 2018	Berge 2018	Taher 2019	Terry 2013[a]	O'Brien 2020[b]	Davis 2021[c]
Case control studies											
Harlow	1992	1.4 (0.9–2.2)	2.8 (1.2–6.4)	1.2 (0.6–2.5)	1.6 (0.8–3.3)		X	X			
Chang	1997	1.34 (0.96–1.85)	1.7 (1.00–2.79)	1.585 (0.97–2.58)		X	X	X	X		
Cook	1997	1.7 (1.1–2.5)	1.2 (0.6–2.3)	0.7 (0.4–1.4)	1.8 (1.1–2.8)	X	X	X			
Wong	1999	1.2 (0.7–2.1)	1.4 (0.7–2.7)	1.5 (0.6–4.0)	1.6 (0.6–4.3)	X	X	X			
Mills	2004	1.77 (1.12–2.81)	1.28 (0.62–2.62)	2.56 (0.89–7.39)	0.63 (0.15–2.64)	X	X	X			
Goodman	2008	1.29 (0.82, 2.03)	0.49 (0.20–1.18)	0.82 (0.29–2.30)	1.29 (0.82–2.03)		X		X		
Merritt	2008	1.21 (1.03–1.44)	1.18 (0.81–1.70)	1.10 (0.80–1.52)	1.08 (0.68–1.72)	X	X	X	X		
Gates	2008	1.60 (1.26–2.02)	1.41 (0.97–2.05)	1.28 (0.85–1.92)				X			
Moorman	2009	1.56 (1.13–2.15)	1.19 (0.69–2.06)	0.87 (0.27–1.84)	1.03 (0.52–2.03)		X	X	X		X
Rosenblatt	2011	1.01 (0.69–1.47)	1.53 (0.91–2.57)	1.78 (0.98–3.23)		X	X	X	X		
Lo-Ciganic	2012	1.12 (0.83–1.52)	1.32 (0.74–2.35)	3.03 (1.28–7.16)	1.75 (0.86–3.55)		X		X		
Cramer	2016	1.42 (1.19, 1.69)	1.38 (1.06–1.80)	0.87 (0.53, 1.44)	1.01 (0.65–1.57)	X	X	X	X		
Schildkraut	2016	1.38 (1.03–1.85)				X	X	X			X
Cohort studies											
Gertig	2000	1.26 (0.94–1.69)	0.91 (0.49–1.87)	0.93 (0.53–1.66)		X		X		X	
Gates	2010	1.06 (0.84–1.35)	1.06 (0.66–1.69)	1.50 (0.84–2.66)			X			X	
Houghton	2014	1.16 (0.88–1.53)	1.29 (0.64–2.61)	1.03 (0.47–2.27)	1.04 (0.70–1.54)	X	X	X		X	X
Pooled/meta-analyzed estimates											
Penninkilampi	2018	1.32 (1.22–1.43)	1.35 (1.14–1.60)	1.12 (0.94, 1.33)	1.02 (0.75, 1.39)						
Berge	2018	1.24 (1.15–1.34)	1.15 (0.91–1.39)	0.96 (0.73–1.18)	0.98 (0.72–1.23)						
Taher	2019	1.35 (1.21–1.50)		1.17 (0.82–1.67)							
Terry	2013	1.20 (1.09–1.32)	1.22 (1.04–1.43)	1.09 (0.84–1.42)	1.24 (1.01–1.52)						
O'Brien	2020	1.10 (0.97–1.25)	1.15 (0.83–1.58)	1.03 (0.69–1.54)	1.17 (0.73–1.89)						
Davis, African Americans	2021	1.30 (1.00–1.68)									
Davis, Whites	2021	1.32 (1.13–1.56)									

[a] Additionally includes data from the University of Southern California Study of Lifestyle and Women's Health [62].
[b] Additionally includes data from the Nurses Health Study II (talc data previously unpublished) and the Sister Study [42].
[c] Additionally includes data from the University of Southern California Study of Lifestyle and Women's Health [62] and the Cook County Case-Control Study (talc data previously unpublished).

0.73–1.18) or clear cell (RR = 0.98; 95% CI: 0.72–1.23) [30]. A positive association with serous tumors was again demonstrated in the Taher et al. meta-analysis (OR = 1.35, 95% CI: 1.21–1.50) [31]. Taher et al. observed an elevated but not significant risk associated with mucinous tumors (OR = 1.17, 95% CI: 0.82–1.67). In the Terry et al. pooled analysis, ever genital powder use was associated with serous (OR = 1.20, 95% CI: 1.09–1.32), endometroid (OR = 1.22, 95% CI: 1.04–1.43) and clear cell (OR = 1.24, 95% CI:1.01–1.52) carcinomas, but not mucinous (OR = 1.09, 95% CI: 0.84–1.42) [34].

In the pooled analysis that included updated data from the prospective cohorts, O'Brien et al. observed an elevated but not statistically significant hazard ratio for the association between ever genital powder use and serous ovarian cancers (HR = 1.10, 95% CI: 0.97–1.25) [32]. Estimates were also elevated for endometroid (HR = 1.15, 95% CI: 0.83–1.58) and clear cell (HR = 1.17, 95% CI: 0.73–1.89) carcinomas, but not statistically significant. Ever genital powder use was not associated with mucinous tumors (HR = 1.03, 95% CI: 0.69–1.54). The Davis et al. pooled analyses also reported elevated risk for serous tumors in both African American (OR = 1.30, 95% CI: 1.00–1.68) and white women (OR = 1.32, 95% CI: 1.13–1.56). The other histotypes were not separately evaluated [63].

Overall, these results consistently demonstrate that there is a positive association between talc use and serous ovarian cancers, and possibly also endometroid tumors. The relationship between talc use and the rarer mucinous or clear cell tumor histotypes is more ambiguous, though it is not clear whether this is due to true etiologic differences or because their rarity makes them more difficult to study.

5.3. Associations of genital powder use and ovarian cancer risk by tubal ligation and hysterectomy status

Another key factor in understanding the potentially causal relationship between talc use and ovarian cancer is the concept of patency, defined here as having an unobstructed physical pathway between the genital area and ovaries. The proposed carcinogenic mechanism suggests that talc particles must travel up the reproductive tract (through the vagina, cervix, and uterus) to reach the fallopian tubes and ovaries. As such, it would make sense that women who did not have uteri (i.e. had had a hysterectomy) and/or those who had blocked fallopian tubes (via tubal ligation), would have a markedly reduced risk of developing the disease as a direct consequence of talc use. As described below, many of the existing studies have attempted to look at this in some way. However, most were unable to do so with a clear temporal sequence between hysterectomy/tubal ligation and powder use. For example, it may not be possible to know whether talc was used prior to hysterectomy/tubal ligation or what a woman's combined patency

Table 3
Reported estimates of the association between ever (versus never) powder use and ovarian cancer stratified by hysterectomy and tubal ligation (TL) status, including summary estimates from published meta- and pooled analyses.

Author	Year	Association for ever vs. never talc use		Notes	Taher 2019 meta-analysis	Terry 2013 pooled[a]	O'Brien 2020[b] pooled
		Patent women (no hysterectomy or tubal ligation)	Women with hysterectomy and/or tubal ligation (non-patent)				
Case control studies							
Cramer	1982	2.79 ($p < 0.003$)		compared to 3.28 overall	X		
Whittemore	1988	1.33 (0.88, 2.01)	1.42 (0.75, 2.68)	non-patent estimate based on crude numbers	X		
Harlow	1992	1.7 (1.0–3.0) for 10,000 applications versus none		compared to 1.8 (1.0, 3.0) overall	X		
Rosenblatt	1992	2.4 (1.0–5.8)	0.15 (0.027–0.88)	tubal ligation only; patency estimates based on talc use prior to tubal ligation/ never tubal ligation, non-patent estimate based on time after tubal ligation	X		
Green	1997	1.3 (1.0–1.7)	0.6 (0.5–0.84)	patency estimates based on talc use prior to surgery/ never surgery, non-patent estimate based on time after surgery	X		
Chang	1997	1.11 (0.99–1.24)	1.03 (0.82–1.29)		X	X	
Cook	1997			estimates unchanged after excluding those who used powder after hysterectomy/tubal ligation	X		
Wong	1999	1.2 (0.8–1.6)	0.8 (0.5–1.2)		X		
Mills	2004	1.54 (1.10–2.16) no TL; 1.33 (0.95–1.87) no hyst	0.88 (0.46–1.68) TL; 1.79 (0.91–3.52) hyst		X		
Merritt	2008	>25 years vs. none: 1.29 (1.04–1.58), p-trend =0.02	>25 years vs. none: 1.00 (0.64–1.51); p-trend = 0.61	patency estimates based on talc use prior to surgery/ never surgery, non-patent estimate based on time after surgery	X	X	
Rosenblatt	2011	1.23 (0.93–1.64)		compared to 1.27 (0.97, 1.66) overall	X	X	
Cramer	2016	1.22 (1.04, 1.43)	1.73 (1.31, 2.27)		X	X	
Cohort studies							
Gertig	2000	1.16 (1.01–1.33)	1.07 (0.94–1.20)	updated study-specific results from O'Brien et al.	X		X
Houghton	2014	1.13 (1.01–1.26)	1.11 (0.95–1.30)	updated study-specific results from O'Brien et al.	X		X
Gonzalez	2016	0.85 (0.92–1.39)	1.02 (0.76–1.38)	updated study-specific results from O'Brien et al.	X		X
Pooled/Meta-analyzed estimates							
Taher	2019		1.06 (0.78, 1.42)	compared to 1.06 (0.90–1.25) overall			
Terry	2013	Q5 vs. Q1 of cumulative applications: 1.36 (1.18–1.57)		Limiting analysis to those exposed prior to surgery (or never surgery) made "no substantive difference" in results			
O'Brien	2020	1.13 (1.01–1.26)	0.99 (0.86–1.15)				
Davis[c]	2021	1.27 (1.09–1.48)	1.42 (1.17–1.72)				

[a] Additionally includes data from the University of Southern California Study of Lifestyle and Women's Health [62]; the Hawaii Ovarian Cancer Study [43]; the North Carolina Ovarian Cancer Study [53]; the Hormones and Ovarian Cancer Prediction Study [50].
[b] Additionally includes data from the Nurses Health Study II (talc data previously unpublished) and the Sister Study [42].
[c] Includes only Women's Health Initiative [48] from table. Additionally includes data from the University of Southern California Study of Lifestyle and Women's Health [62], the Cook County Case-Control Study (talc data previously unpublished), North Carolina Ovarian Cancer Study [53] and the African-American Cancer Epidemiology Study [28].

and talc use status was during key windows of susceptibility (e.g. menopause).

In their pooled analysis of 8 case-control studies, Terry et al. found that after excluding those who first started using genital powder after hysterectomy or tubal ligation, results were similar to the overall analysis (Table 3; OR = 1.36, 95% CI: 1.18–1.57 for the 4th versus 1st quartile of cumulative number of lifetime talc applications; compared to original overall estimate OR = 1.32, 95% CI: 1.16–1.52) [34]. The only meta-analysis to explore this issue was Taher et al., who reported an inverse association between talc and ovarian cancer among those who had had tubal ligation (OR = 0.64, 95% CI: 0.45–0.92) [31]. When they examined studies that reported estimates from participants with a history of either hysterectomy or tubal ligation, the meta-analyzed estimate was close to null (OR = 1.06, 95% CI: 0.78–1.42). Davis et al. reported similar estimates when analyses were restricted to women with patent reproductive tracts (OR = 1.27, 95% CI: 1.09–1.48) versus those with a history of tubal ligation or hysterectomy (OR = 1.42, 95% CI: 1.17–1.72; p-for-heterogeneity = 0.31) [63].

The prospective studies did not systematically collect details on timing of genital powder use relative to the age at which women underwent hysterectomy or tubal ligation [32]. However, in those who had patent reproductive tracts at enrollment, a history of genital powder use was associated with an increased risk of developing incident ovarian cancer (HR = 1.13, 95% CI: 1.01–1.26). This association was null among women who did not have patent reproductive tracts at enrollment (HR = 0.99, 95% CI: 0.86–1.15).

Given the difficulties with establishing a clear sequence of events in the genital powder use relative to hysterectomy or tubal ligation, especially in the case-control studies, the interpretation of these findings is quite difficult. However, the results of the prospective studies support the hypothesis that the positive association between genital powder use and ovarian cancer may be limited to women with patent reproductive tracts.

5.4. Associations of genital powder use and ovarian cancer risk in diverse populations

As previously mentioned, Davis et al. conducted a pooled analysis examining the association between genital powder use and ovarian cancer in the OCWAA consortium [63], which only included studies with large samples of African-American women. Consistent with previously observed trends, African American women in the included studies were more likely to report ever having used genital powder (34% of African-American non-cases versus 31% of White non-cases), but effect estimates were similar between the two racial groups (OR = 1.22, 95% CI: 0.97–1.53 in African American women and OR = 1.37, 95% CI: 1.1–1.57 in White women). In analyses limited to high grade serous tumors, Davis et al. reported elevated associations for both African American (OR = 1.30. 95% CI: 1.00–1.68) and White (OR = 1.32, 95% CI: 1.13–1.56) women. Non-serous tumors were positively associated with powder use in White women (OR = 1.38, 95% CI: 1.15–1.66), but not African American women (OR = 1.08. 95% CI: 0.78–1.51).

5.5. Association of genital powder use and uterine cancer

The shared etiology of ovarian and uterine cancer subtypes warrant evaluation of presumed and established ovarian cancer risk factors in uterine cancer studies. Genital powder has easier access to the uterine lining compared to the fallopian tubes and the ovarian surface. On the other hand, menstruation could clear genital powder from the surface of the uterus, thereby mitigating its influence. Several studies have evaluated the association of genital powder use and uterine cancer, including one case-control study [64] and three cohort studies [65–67]. Updated data from the three cohorts plus the Nurses' Health Study II were combined in a uterine-cancer specific pooled analysis [26].

The case-control study reported no association between perineal talc use and endometrial cancer (OR = 0.88, 95% CI: 0.68–1.14) [64]. Findings from the pooled analysis were also null (HR = 1.01, 95% CI: 0.94–1.09), except for a possible increased risk among long-term users (>20 years; HR = 1.12, 95% CI: 0.96–1.31). There was no evidence for heterogeneity by endometrial cancer subtype.

6. Conclusion

When assessing the complex relationship between genital powder use and ovarian cancer, three important related questions need to be addressed: 1. Is there an association between genital powder and ovarian cancer risk? 2. If there is an association, what is the underlying causal factor? 3. If there is an association, what is the clinical and public health relevance? The epidemiological data on the association between powder use and ovarian cancer risk have varied by study type. Recent systematic reviews and meta-analyses that included case-control data reported elevated ovarian cancer risk among powder users relative to non-users, with odds ratios ranging from 1.22 to 1.32. Concern has been raised that this association could be at least somewhat attributable to recall bias, which would occur if ovarian cancer patients were more likely to report body powder use compared to controls [29].

Because cohort studies assess exposure before disease occurs, they are not subject to recall bias. Individual cohort studies have not shown statistically significant associations between powder use and ovarian cancer risk, but many cohort studies are limited by low ovarian cancer case numbers and limited exposure assessments. In a recent pooled cohort analysis with a large number of cases, ever use of genital powder was positively associated with ovarian cancer, but the hazard ratio did not reach statistical significance. However, a pre-specified sub-analysis limited to women who had not had a hysterectomy or tubal ligation showed a statistically significant positive association (HR = 1.13). Taken together, the epidemiological data from case-control studies and cohort studies suggest that there may be a small, positive association between genital powder use and ovarian cancer, which may be limited to women with patent reproductive tracts. Data from a large case-control study suggested that associations between talc use and ovarian cancer risk were largely confined to premenopausal women and postmenopausal women who used hormone therapy [39]. This could indicate that estrogen may be an effect modifier of the talc-ovarian cancer association.

The inability to differentiate between different types of powder and their respective ingredients in epidemiological studies makes it challenging to identify factors responsible for the observed associations. Since talc is a major component in many body powders, it has long been proposed as a causal factor. However, the experimental and animal carcinogenicity data for talc are limited and inconclusive, and there are currently no good animal or experimental models of ovarian carcinogenesis that could be used to more directly test biological effects of talc [1]. Asbestos contamination of talc was proposed as an explanation for some of the initially observed associations between powder use and ovarian cancer, and recent findings of asbestos contamination in cosmetic products suggest that asbestos could have continued to play a role. Data on other possibly carcinogenic contaminants of talc, such as quartz, are very scarce. Other components of body powder, including corn starch, could also possibly play a role in carcinogenesis by inducing inflammation in the reproductive tract, but carcinogenicity data are lacking. Confounding by indication may explain some of the observed associations. This would occur if women with hormonal or inflammatory exposures or conditions that are associated with ovarian cancer were also more likely to use powder in the genital area. However, there is currently no data supporting such an effect. In summary, we currently do not understand the causal factors that underly the observed weak associations between genital powder use and ovarian cancer risk.

Independent of the underlying cause, the association between powder use and ovarian cancer risk is weak. The low relative risk translates to a very low absolute risk increase, given the rarity of ovarian cancer. In the pooled cohort analysis by O'Brien et al., the estimated increase in ovarian cancer risk by age 70 was 0.09% (95% CI: −0.02-0.19%) for all users of body powder and 0.22% (95% CI: 0.02–0.42%) for body powder users with patent reproductive tracts [32]. Given the inability to attribute a clear causal factor to the observed associations, the lack of a good experimental model, the lack of a specific biomarker for powder-related carcinogenesis, and the inability to rule out confounding by indication, it is difficult to conclude that the observed associations are causal. Furthermore, given the widespread use of powders and the rarity of ovarian cancer, the case for public health relevance is limited.

Future work on understanding the association of powder use and ovarian cancer risk should focus both on existing data and new studies. Given that the association from case-control studies may be exaggerated by recall bias and the association from cohort studies may be underestimated because of limited exposure information and attenuation in effects over time since exposure assessment, the association probably lies between these estimates. A systematic bias assessment could attempt to account for these biases and lead to a more accurate risk estimate. Existing studies may have collected more detailed exposure information, particularly on timing of powder use and brand names that could allow investigators to revisit the role of possible asbestos contamination of cosmetic talc products. Further, data on additional medical conditions that may be related both to ovarian cancer risk and powder use may be available in these studies, allowing for further evaluation of confounding by indication. Future studies should expand on the assessment of body powder use, with an extended focus that captures data on different formulations, including talc-free brands and improved exposure quantification. Ideally, this would also include careful consideration of differences in product use across different racial/ethnic groups, given the observed higher use of genital powder among African American women [63]. Biological and experimental studies on potential mechanisms of powder-related carcinogenesis should also focus more on extra-ovarian cells of origin, particularly in the fallopian tubes. Further, biological studies should evaluate other components of body powders, such as corn starch, that may cause inflammatory reactions in the genital tract and the fallopian tubes. Despite the limitations of current experimental and animal models that complicate evaluating the full carcinogenic process, the effects of body powder components on inflammation in various areas of the genital tract could provide important data on intermediate endpoints that could explain potential carcinogenic mechanisms.

Use of talcum powder has decreased substantially in the US over the last decades [68]. Following the recent reports on asbestos contamination of talc products, the cosmetic industry has moved away from using talc in their products and major brands of talcum powder have been removed from the market. Given the weak observed associations and the uncertainty of the underlying causes, current recommendations about body powder use remain vague. For example, the American Cancer Society states that “Until more information is available, people concerned about using talcum powder may want to avoid or limit their use of consumer products that contain it.” [69] Given the uncertainty about the role of other powder ingredients in the observed associations and continued widespread use of body powder around the world, we should continue to evaluate the health effects of genital powder use, as well as the public health messaging related to powder use.

Author contributions

Nicolas Wentzensen: Conceptualization; Data curation; Investigation; Methodology; Writing - original draft, review & editing. *Katie O'Brien*: Conceptualization; Data curation; Investigation; Methodology; Writing - original draft, review & editing.

Funding statement

This work was supported the Intramural Research Program of the National Institutes of Health (National Cancer Institute and National Institute of Environmental Health Sciences).

Declaration of Competing Interest

The authors do not report a conflict of interest.

References

[1] IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, Carbon black, titanium dioxide, and talc, IARC Monogr. Eval. Carcinog. Risks Hum. 93 (2010) 1–413.
[2] IARC monographs on the evaluation of the carcinogenic risk of chemicals to man: asbestos, IARC Monogr. Eval. Carcinog. Risk Chem. Man. 14 (1977) 1–106.
[3] S.A. Narod, Talc and ovarian cancer, Gynecol. Oncol. 141 (3) (2016) 410–412.
[4] W.J. Henderson, C.A. Joslin, A.C. Turnbull, K. Griffiths, Talc and carcinoma of the ovary and cervix, J. Obstet. Gynaecol. Br. Commonw. 78 (3) (1971) 266–272.
[5] D.L. Longo, R.C. Young, Cosmetic talc and ovarian cancer, Lancet 2 (8138) (1979) 349–351.
[6] D.W. Cramer, W.R. Welch, R.E. Scully, C.A. Wojciechowski, Ovarian cancer and talc: a case-control study, Cancer 50 (2) (1982) 372–376.
[7] IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, Arsenic, metals, fibres, and dusts, IARC Monogr. Eval. Carcinog. Risks Hum. 100 (Pt C) (2012) 11–465.
[8] A.N. Rohl, A.M. Langer, I.J. Selikoff, et al., Consumer talcums and powders: mineral and chemical characterization, J. Toxicol. Environ. Health 2 (2) (1976) 255–284.
[9] https://www.fda.gov/cosmetics/cosmetics-recalls-alerts/fda-advises-consumers-stop-using-certain-cosmetic-products 2021.
[10] F.D. Pooley, An examination of the fibrous mineral content of asbestos lung tissue from the Canadian chrysotile mining industry, Environ. Res. 12 (3) (1976) 281–298.
[11] N. Keskin, Y.A. Teksen, E.G. Ongun, Y. Ozay, H. Saygili, Does long-term talc exposure have a carcinogenic effect on the female genital system of rats? An experimental pilot study, Arch. Gynecol. Obstet. 280 (6) (2009) 925–931.
[12] S.A. McDonald, Y. Fan, W.R. Welch, D.W. Cramer, J.J. Godleski, Migration of talc from the perineum to multiple pelvic organ sites, Am. J. Clin. Pathol. 152 (5) (2019) 590–607.
[13] D.W. Cramer, L. Titus-Ernstoff, J.R. McKolanis, et al., Conditions associated with antibodies against the tumor-associated antigen MUC1 and their relationship to risk for ovarian cancer, Cancer Epidemiol. Biomark. Prev. 14 (5) (2005) 1125–1131.
[14] M.A. Gates, S.S. Tworoger, K.L. Terry, et al., Talc use, variants of the GSTM1, GSTT1, and NAT2 genes, and risk of epithelial ovarian cancer, Cancer Epidemiol. Biomark. Prev. 17 (9) (2008) 2436–2444.
[15] R.J. Kurman, Ie M. Shih, The dualistic model of ovarian carcinogenesis: revisited, revised, and expanded, Am. J. Pathol. 186 (4) (2016) 733–747.
[16] N. Wentzensen, E.M. Poole, B. Trabert, et al., Ovarian cancer risk factors by histologic subtype: an analysis from the ovarian cancer cohort consortium, J. Clin. Oncol. 34 (24) (2016) 2888–2898.
[17] R.C. Wu, P. Wang, S.F. Lin, et al., Genomic landscape and evolutionary trajectories of ovarian cancer precursor lesions, J. Pathol. 248 (1) (2019) 41–50.
[18] A.C. Berger, A. Korkut, R.S. Kanchi, et al., A comprehensive pan-cancer molecular study of gynecologic and breast cancers, Cancer Cell 33 (4) (2018) 690–705 (e9).
[19] V.W. Setiawan, H.P. Yang, M.C. Pike, et al., Type I and II endometrial cancers: have they different risk factors? J. Clin. Oncol. 31 (20) (2013) 2607–2618.
[20] H.P. Yang, N. Wentzensen, B. Trabert, et al., Endometrial cancer risk factors by 2 main histologic subtypes: the NIH-AARP diet and health study, Am. J. Epidemiol. 177 (2) (2013) 142–151.
[21] S. Wacholder, Design issues in case-control studies, Stat. Methods Med. Res. 4 (4) (1995) 293–309.
[22] S. Wacholder, J.K. McLaughlin, D.T. Silverman, J.S. Mandel, Selection of controls in case-control studies. I. Principles, Am. J. Epidemiol. 135 (9) (1992) 1019–1028.
[23] G.A. Colditz, Overview of the epidemiology methods and applications: strengths and limitations of observational study designs, Crit. Rev. Food Sci. Nutr. 50 (Suppl. 1) (2010) 10–12.
[24] N. Wentzensen, S. Wacholder, From differences in means between cases and controls to risk stratification: a business plan for biomarker development, Cancer Discov. 3 (2) (2013) 148–157.
[25] S. Greenland, Validity and bias in epidemiological research, in: R. Detels, R. Beaglehole, M.A. Lansang, M. Gulliford (Eds.), Oxford Textbook of Public Health, 6th edOxford University Press, 2009.
[26] K.M. O'Brien, S.S. Tworoger, H.R. Harris, et al., Genital powder use and risk of uterine cancer: a pooled analysis of prospective studies, Int. J. Cancer 148 (11) (2021) 2692–2701.
[27] N. Wentzensen, S. Wacholder, Talc use and ovarian cancer: epidemiology between a rock and a hard place, J. Natl. Cancer Inst. 106 (9) (2014).
[28] J.M. Schildkraut, S.E. Abbott, A.J. Alberg, et al., Association between body powder use and ovarian cancer: the African American Cancer epidemiology study (AACES), Cancer Epidemiol. Biomark. Prev. 25 (10) (2016) 1411–1417.
[29] B. Trabert, Body powder and ovarian cancer risk-what is the role of recall bias? Cancer Epidemiol. Biomark. Prev. 25 (10) (2016) 1369–1370.

[30] W. Berge, K. Mundt, H. Luu, P. Boffetta, Genital use of talc and risk of ovarian cancer: a meta-analysis, Eur. J. Cancer Prev. 27 (3) (2018) 248–257.
[31] M. Kadry Taher, N. Farhat, N.A. Karyakina, et al., Critical review of the association between perineal use of talc powder and risk of ovarian cancer, Reprod. Toxicol. 90 (2019) 88–101.
[32] K.M. O'Brien, S.S. Tworoger, H.R. Harris, et al., Association of powder use in the genital area with risk of ovarian cancer, JAMA 323 (1) (2020) 49–59.
[33] R. Penninkilampi, G.D. Eslick, Perineal talc use and ovarian cancer: a systematic review and meta-analysis, Epidemiology 29 (1) (2018) 41–49.
[34] K.L. Terry, S. Karageorgi, Y.B. Shvetsov, et al., Genital powder use and risk of ovarian cancer: a pooled analysis of 8,525 cases and 9,859 controls, Cancer Prev. Res. (Phila.) 6 (8) (2013) 811–821.
[35] M. Booth, V. Beral, P. Smith, Risk factors for ovarian cancer: a case-control study, Br. J. Cancer 60 (4) (1989) 592–598.
[36] S. Chang, H.A. Risch, Perineal talc exposure and risk of ovarian carcinoma, Cancer 79 (12) (1997) 2396–2401.
[37] Y. Chen, P.C. Wu, J.H. Lang, W.J. Ge, P. Hartge, L.A. Brinton, Risk factors for epithelial ovarian cancer in Beijing, China, Int. J. Epidemiol. 21 (1) (1992) 23–29.
[38] L.S. Cook, M.L. Kamb, N.S. Weiss, Perineal powder exposure and the risk of ovarian cancer, Am. J. Epidemiol. 145 (5) (1997) 459–465.
[39] D.W. Cramer, A.F. Vitonis, K.L. Terry, W.R. Welch, L.J. Titus, The association between talc use and ovarian cancer: a retrospective case-control study in two US states, Epidemiology 27 (3) (2016) 334–346.
[40] D.M. Gertig, D.J. Hunter, D.W. Cramer, et al., Prospective study of talc use and ovarian cancer, J. Natl. Cancer Inst. 92 (3) (2000) 249–252.
[41] B. Godard, W.D. Foulkes, D. Provencher, et al., Risk factors for familial and sporadic ovarian cancer among French Canadians: a case-control study, Am. J. Obstet. Gynecol. 179 (2) (1998) 403–410.
[42] N.L. Gonzalez, K.M. O'Brien, A.A. D'Aloisio, D.P. Sandler, C.R. Weinberg, Douching, talc use, and risk of ovarian cancer, Epidemiology 27 (6) (2016) 797–802.
[43] M.T. Goodman, G. Lurie, P.J. Thompson, K.E. McDuffie, M.E. Carney, Association of two common single-nucleotide polymorphisms in the CYP19A1 locus and ovarian cancer risk, Endocr. Relat. Cancer 15 (4) (2008) 1055–1060.
[44] A. Green, D. Purdie, C. Bain, et al., Tubal sterilisation, hysterectomy and decreased risk of ovarian cancer. Survey of women's health study group, Int. J. Cancer 71 (6) (1997) 948–951.
[45] B.L. Harlow, D.W. Cramer, D.A. Bell, W.R. Welch, Perineal exposure to talc and ovarian cancer risk, Obstet. Gynecol. 80 (1) (1992) 19–26.
[46] B.L. Harlow, N.S. Weiss, A case-control study of borderline ovarian tumors: the influence of perineal exposure to talc, Am. J. Epidemiol. 130 (2) (1989) 390–394.
[47] P. Hartge, R. Hoover, L.P. Lesher, L. McGowan, Talc and ovarian cancer, JAMA 250 (14) (1983) 1844.
[48] S.C. Houghton, K.W. Reeves, S.E. Hankinson, et al., Perineal powder use and risk of ovarian cancer, J. Natl. Cancer Inst. 106 (9) (2014).
[49] M.L. Kurta, K.B. Moysich, J.L. Weissfeld, et al., Use of fertility drugs and risk of ovarian cancer: results from a U.S.-based case-control study, Cancer Epidemiol. Biomark. Prev. 21 (8) (2012) 1282–1292.
[50] W.H. Lo-Ciganic, J.C. Zgibor, C.H. Bunker, K.B. Moysich, R.P. Edwards, R.B. Ness, Aspirin, nonaspirin nonsteroidal anti-inflammatory drugs, or acetaminophen and risk of ovarian cancer, Epidemiology 23 (2) (2012) 311–319.
[51] M.A. Merritt, A.C. Green, C.M. Nagle, P.M. Webb, Australian Cancer S, Australian Ovarian Cancer Study G, Talcum powder, chronic pelvic inflammation and NSAIDs in relation to risk of epithelial ovarian cancer, Int. J. Cancer 122 (1) (2008) 170–176.
[52] P.K. Mills, D.G. Riordan, R.D. Cress, H.A. Young, Perineal talc exposure and epithelial ovarian cancer risk in the Central Valley of California, Int. J. Cancer 112 (3) (2004) 458–464.
[53] P.G. Moorman, R.T. Palmieri, L. Akushevich, A. Berchuck, J.M. Schildkraut, Ovarian cancer risk factors in African-American and white women, Am. J. Epidemiol. 170 (5) (2009) 598–606.
[54] R.B. Ness, J.A. Grisso, C. Cottreau, et al., Factors related to inflammation of the ovarian epithelium and risk of ovarian cancer, Epidemiology 11 (2) (2000) 111–117.
[55] D. Purdie, A. Green, C. Bain, et al., Reproductive and other factors and risk of epithelial ovarian cancer: an Australian case-control study. Survey of Women's Health Study Group, Int. J. Cancer 62 (6) (1995) 678–684.
[56] K.A. Rosenblatt, M. Szklo, N.B. Rosenshein, Mineral fiber exposure and the development of ovarian cancer, Gynecol. Oncol. 45 (1) (1992) 20–25.
[57] K.A. Rosenblatt, N.S. Weiss, K.L. Cushing-Haugen, K.G. Wicklund, M.A. Rossing, Genital powder exposure and the risk of epithelial ovarian cancer, Cancer Causes Control 22 (5) (2011) 737–742.
[58] A. Shushan, O. Paltiel, J. Iscovich, U. Elchalal, T. Peretz, J.G. Schenker, Human menopausal gonadotropin and the risk of epithelial ovarian cancer, Fertil. Steril. 65 (1) (1996) 13–18.
[59] A. Tzonou, A. Polychronopoulou, C.C. Hsieh, A. Rebelakos, A. Karakatsani, D. Trichopoulos, Hair dyes, analgesics, tranquilizers and perineal talc application as risk factors for ovarian cancer, Int. J. Cancer 55 (3) (1993) 408–410.
[60] A.S. Whittemore, M.L. Wu, R.S. Paffenbarger Jr., et al., Personal and environmental characteristics related to epithelial ovarian cancer. II. Exposures to talcum powder, tobacco, alcohol, and coffee, Am. J. Epidemiol. 128 (6) (1988) 1228–1240.
[61] C. Wong, R.E. Hempling, M.S. Piver, N. Natarajan, C.J. Mettlin, Perineal talc exposure and subsequent epithelial ovarian cancer: a case-control study, Obstet. Gynecol. 93 (3) (1999) 372–376.
[62] A.H. Wu, C.L. Pearce, C.C. Tseng, M.C. Pike, African Americans and Hispanics remain at lower risk of ovarian cancer than non-Hispanic Whites after considering nongenetic risk factors and oophorectomy rates, Cancer Epidemiol. Biomark. Prev. 24 (7) (2015) 1094–1100.
[63] C.P. Davis, E.V. Bandera, T.N. Bethea, et al., Genital powder use and risk of epithelial ovarian cancer in the Ovarian Cancer in Women of African Ancestry Consortium, Cancer Epidemiol. Biomark. Prev. (2021) Online ahead of print.
[64] A.S. Neill, C.M. Nagle, A.B. Spurdle, P.M. Webb, Use of talcum powder and endometrial cancer risk, Cancer Causes Control 23 (3) (2012) 513–519.
[65] L. Crawford, K.W. Reeves, N. Luisi, R. Balasubramanian, S.R. Sturgeon, Perineal powder use and risk of endometrial cancer in postmenopausal women, Cancer Causes Control 23 (10) (2012) 1673–1680.
[66] S. Karageorgi, M.A. Gates, S.E. Hankinson, I. De Vivo, Perineal use of talcum powder and endometrial cancer risk, Cancer Epidemiol. Biomark. Prev. 19 (5) (2010) 1269–1275.
[67] K.M. O'Brien, A.A. D'Aloisio, M. Shi, J.D. Murphy, D.P. Sandler, C.R. Weinberg, Perineal talc use, douching, and the risk of uterine cancer, Epidemiology 30 (6) (2019) 845–852.
[68] T.D. Kelly, G.R. Matos, Historical Statistics for Mineral and Material Commodities in the United States, https://www.usgs.gov/centers/nmic/historical-statistics-mineral-and-material-commodities-united-states 2017.
[69] American Cancer Society, Talcum Powder and Cancer, https://www.cancer.org/content/dam/CRC/PDF/Public/664.00.pdf February 4, 2020.

EXHIBIT 15

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF NEW JERSEY

IN RE JOHNSON & JOHNSON TALCUM POWDER PRODUCTS MARKETING, SALES PRACTICES, AND PRODUCTS LIABILITY LITIGATION	)	MDL NO. 16-2738(FLW)(LHG)

IN THE CIRCUIT COURT OF THE CITY OF ST. LOUIS
STATE OF MISSOURI

VALERIE SWANN, Plaintiff, v. JOHNSON & JOHNSON, et al., Defendants.	)	Cause No. 1422-CC09326-03

__ __ __

Tuesday, September 14, 2021

__ __ __

Oral Deposition of JUDITH WOLF, M.D., VOLUME 2, held at the Fairmont Hotel, 101 Red River Street, Austin, Texas, commencing at 8:53 a.m. CDT, on the above date, before Michael E. Miller, Fellow of the Academy of Professional Reporters, Certified Court Reporter, Registered Diplomate Reporter, Certified Realtime Reporter and Notary Public.

__ __ __

GOLKOW LITIGATION SERVICES
877.370.DEPS | fax 917.591.5672
deps@golkow.com

although her genetic testing was negative, she did have a family history of cancer that was significant.

Q. Any other contributing causes for Ms. Bondurant's clear-cell ovarian cancer?

A. She gave a history of [redacted].

Q. If, in fact, she did have [redacted], that would be a contributing cause as well, correct?

A. It would be a risk factor.

Q. Any other contributing causes or -- and let me stop there.

We talked yesterday, and I believe you agreed, that there is a difference between a risk factor and cause; is that right?

A. Yes.

Q. You believe that in her case,

that talcum powder is a substantial contributing cause, correct?

A. Yes. Yes.

Q. She does have other risk factors which may be contributing causes.

Is that a fair summary of your testimony?

A. Well, she had -- her other risk factor [redacted].

Q. And that's [redacted]; is that right?

A. Yes.

Q. And [redacted]?

A. I'm just trying to find her family history in my report.

Q. Page 24, I believe.

A. Yes. [redacted].

Q. [redacted]?

A. [redacted].

Q. That is not a risk factor?

confirmation of that or surgical confirmation.

Q. As we talked yesterday, [redacted]; is that right?

A. [redacted].

Q. [redacted]

That's on page 24 of your report. Is that right?

DR. THOMPSON: Object to form.

A. That's not what I -- it says. I said [redacted] --

BY MR. ZELLERS:

Q. The quote I have on page 24 of your report is [redacted].

that or not include that.

Q. Well, you're aware that Ms. Bondurant herself, before she passed, reported that [redacted]?

A. Yes.

Q. She also reported [redacted]; is that right?

A. Yes.

Q. Wouldn't Ms. Bondurant have been a reliable source of information as to [redacted]?

DR. THOMPSON: Object to form.

A. [redacted].

BY MR. ZELLERS:

Q. [redacted]?

we can do about it.

Q. I think I saw in your earlier testimony that you believe the latency period from ovarian cancer can be anywhere from 15 to 20 years; is that right?

A. Yes.

DR. THOMPSON: Object to form.

A. That's a different question, though. That's how long does an exposure that can be carcinogenic, how long does that take until the cancer is there?

I think that's a different question than you asked me before.

BY MR. ZELLERS:

Q. And that would be -- what you just described would be the latency --

A. No. What I described is once there's a cancer, how long has it been there until it's found? That's what I was describing.

Q. And you believe that would be the latency period?

A. No, the latency period is the time of the exposure until the cell becomes cancerous.

DR. THOMPSON: Object to form.

A. What I'm saying is some women who get ovarian cancer have never used talc, and in Ms. Judkins' case, she got ovarian cancer and she used talc.

BY MR. ZELLERS:

Q. Ms. Judkins was 60 years old at her diagnosis?

A. Yes.

Q. Could Ms. Judkins' age -- well, let me withdraw that.

Was Ms. Judkins' age a risk factor for ovarian cancer?

A. Advancing age can always be a risk factor. She is slightly younger than the average age, so I wouldn't separate it out in her case as a risk factor.

I think I talked yesterday about an example of ninety -- I've had women in their nineties, and then I would definitely call age a risk factor.

Q. Age generally does increase a woman's risk for mutations, correct?

A. Age increases anyone's risk for mutations.

[redacted].

Q. [redacted] would be a risk factor for the development of ovarian cancer, correct?

DR. THOMPSON: Object to form.

A. No. No. One -- [redacted]

[redacted].

BY MR. ZELLERS:

Q. Could Ms. Judkins' [redacted] have played a role in her development of ovarian cancer?

DR. THOMPSON: Object to form.

A. It's unlikely.

BY MR. ZELLERS:

Q. You believe that the route of exposure in Ms. Judkins' case was through migration?

A. Yes.

Q. Do you believe that Ms. Judkins' ovarian cancer was caused from talcum powder traveling to her ovaries

that you believe would be relevant in terms of being a cause of ovarian cancer would be [redacted]; is that right?

DR. THOMPSON: Object to form.

A. That's when [redacted], yes.

BY MR. ZELLERS:

Q. In your report, you rely on Dr. Godleski's pathology report in forming your case-specific opinions; is that right?

A. Yes.

Q. Dr. Godleski looked at tissue blocks in Ms. Swann's case.

I'll provide you with Dr. Godleski's report.

A. Thank you.

Q. We'll mark it as Exhibit 51.

(Whereupon, Deposition Exhibit Wolf-51, 4/18/19 Godleski Expert Report re: Swann, was marked for identification.)

BY MR. ZELLERS:

Q. You have Dr. Godleski's report in front of you; is that right?

EXHIBIT 16

UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF NEW JERSEY

MDL-NO. 16-2738 (FLW)(LHG)

IN RE: JOHNSON & JOHNSON TALCUM POWDER PRODUCTS MARKETING, SALES PRACTICES, AND PRODUCTS LIABILITY LITIGATION

ORAL DEPOSITION OF:

DANIEL L. CLARKE-PEARSON, MD

VOLUME 1

* * * *

THURSDAY, AUGUST 26, 2021

* * * *

MASTROIANNI & FORMAROLI, INC.

Certified Court Reporting & Videoconferencing

515 South White Horse Pike

Audubon, New Jersey 08106

856-546-1100

And if you turn to the next page, you have a slide, this is page 17 of the document and 34 of the slide deck, you have a slide devoted to risk factors for ovarian cancer, right?

A. Yes.

Q. And we already saw earlier in your presentation that you defined risk factors as anything that can increase a women's risk of ovarian cancer, right?

A. Right.

Q. And here the first bullet you have is hereditary risk factors, right?

A. Yes.

Q. BRCA1 and BRCA2 gene mutations, right?

What are you writing?

A. I'm just making a few additional notes. You're welcome to look at them.

Q. So, you can tell me what they are when we're done.

A. Sure.

Q. I'm going to guess that you're adding some other risk factors that are not --

A. Yeah, there are a lot of risk factors that we didn't list here.

Q. You did list hereditary, right?

A. Yes. That's important for women to be aware of their family history and knowing that that's the most significant risk factor.

Q. And you did list age, correct?

A. Yes.

Q. And you did list obesity, right?

A. Yes.

Q. And you did list nulliparity, right?

A. Yes.

Q. You did list a family history of breast, ovarian or colon cancer, right?

A. Yes.

Q. You did list personal history of breast cancer, right?

A. Right.

Q. You did not list perineal use of talc?

A. And there is a good number of other risk factors that I didn't list as well. Including polycystic ovarian syndrome, pelvic inflammatory disease, IUD use, endometriosis. We didn't mention Lynch syndrome in the hereditary which is also very important. So there is a number of risk factors that were not listed.

BY MS. BROWN:

Q. By February of 2021, you had been

A. One of the potential causes, yes.

Q. Did you consider Ms. Converse's [redacted] to be a cause of her ovarian cancer?

A. No, because -- let me just take a look at my notes for a minute.

Q. Sure.

A. [redacted].

MS. BROWN: Could we take a look at tab 37, please?

(Exhibit 26, medical record for Hilary Converse, is marked for identification)

BY MS. BROWN:

Q. Doctor, we are going to mark as Exhibit 26 to your deposition a medical record for Hilary Converse. The medical record I've shown you comes from the Smilow Breast Surgery-Yale New Haven Hospital.

Do you see that?

Down at the bottom it says Yale New Haven.

A. I'm sorry. I lost you here. This is a Memorial Sloan-Kettering --

genetic testing, then the answer is no.

Q. It says: She has [redacted].

Do you believe that to be true that [redacted]?

A. I'm not aware of that. Is this an error in the medical record here?

Q. Okay.

Towards the end of this paragraph it says, the last sentence: She [redacted].

Do you see that?

A. Yes.

Q. And you believe the literature supports that [redacted]?

A. In [redacted] only. [redacted] reduces the risk.

Q. You do not believe that [redacted] increased her risk of ovarian cancer?

A. No.

Secondly, she has no past history that would suggest [redacted].

Q. You disagree with her treating physician, Dr. Schwartz's testimony, that [redacted]?

MS. THOMPSON: Objection.

THE WITNESS: I don't disagree with him. It's possible that -- [redacted].

BY MS. BROWN:

Q. But you didn't look at any of her